Evaluation of the introduction of a novel vital sign device in the management of hypertension and shock in pregnancy in low and middle income countries

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Evaluation of the introduction of a novel vital sign device in the management of hypertension and shock in pregnancy in low and middle-income countries

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Acknowledgements

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Thank you also to all my family and friends for their unwavering support, especially my husband, for being my biggest believer. Finally, in memory of my grandmother, Margaret Vousden, who would have been most proud.

Abstract

Background:

In 2015, over 800 women died in pregnancy and childbirth every day. There are effective treatments for the leading causes of maternal death, but they require early detection by measurement of vital signs, and timely administration to save lives. The CRADLE Vital Sign Alert accurately measures blood pressure and pulse and calculates shock index. Results are displayed on a traffic light early warning system. This aim of this thesis was to evaluate the impact of this intervention on maternal mortality and morbidity in low and middle-income countries.

Methods:

A pragmatic, stepped-wedge randomised-controlled trial with a nested mixed-methods process evaluation was undertaken. This was preceded by a mixed-method feasibility study. The intervention was introduced into every level of routine maternity care across 10 clusters in Africa, India and Haiti. The primary composite outcome was at least one of eclampsia, emergency hysterectomy and maternal death per 10,000 deliveries. Delivery of the intervention, its uptake and potential mechanism of action were measured and integrated with qualitative findings and measures of resources and staffing in each cluster.

Findings:

Between April 1st 2016 and November 30th 2017, among 536,223 deliveries, the primary outcome occurred in 4067 women. There was an 8% decrease in the primary outcome from 79.4/10,000 deliveries pre-intervention to 72.8/10,000 post-intervention. After planned adjustments for variation in event rates between and within clusters over time, the unexpected degree of variability meant we were unable to judge the benefit or harms of the intervention (OR 1.22, 95% CI 0.73–2.06; p=0.45). Overall, the intervention was delivered with reasonable fidelity and improved the availability of vital signs equipment and number of women with BP measurements (79.2% vs. 97.6%; OR 1.30, 95% CI 1.29-1.31). There were significant differences in the effect of the intervention between

individual clusters which could not be explained by the measures of implementation or local context.

Interpretation:

The acceptability and feasibility of the intervention has been demonstrated. Despite the rigorous trial design, effectiveness of the intervention at reducing mortality and morbidity has not been shown. Measuring implementation alongside effectiveness was feasible and beneficial in describing differences between clusters in maternal health. In this case, these differences could not explain the difference in the effect of the intervention between individual clusters. Stepped-wedge trials across multiple countries have considerable methodological challenges and should be powered to demonstrate an effect of the intervention in each country. Further research in the selection and integration of process measures in low and middle-income countries is required.

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List of Abbreviations

AUC	Area under curve
BP	Blood pressure
CHW	Community Health Worker
CONSORT	Consolidated Standards of Reporting Trials
dBP	Diastolic BP
EWS	Early Warning System
ICC	Intra-cluster correlation
ICD	International Statistical Classification of Diseases and Related Health Problems
ICU	Intensive Care Unit
HCP	Health care providers
HDP	Hypertensive disorders of pregnancy
HIC	High-income countries
HIV	Human Immunodeficiency Virus
HR	Heart rate
LIC	Low-income countries
LMIC	Low and middle-income countries
MDG	Millennium Development Goals
MEOWS	Modified Early Obstetric Warning System
MMR	Maternal mortality ratio
MRC	Medical Research Council
OR	Odds ratio
PPH	Post-partum Haemorrhage
RCT	Randomised controlled trial
RR	Risk Ratio
SDG	Sustainable Development Goal
SI	Shock Index

SIRS	Systemic Inflammatory Response Syndrome
sBP	Systolic BP
SW-RCT	Stepped Wedge Randomised controlled trial
TIDieR	Template for Intervention Description and Replication
UK	United Kingdom
UNICEF	United Nations Children's Fund
VSA	Vital Sign Alert
WHO	World Health Organisation

Statement of Contribution

This PhD was based around a Medical Research Council funded project entitled 'The CRADLE-3 Trial: Community Blood Pressure Monitoring in Rural Africa and Asia: Detection of UnderLying Pre-Eclampsia and Shock'. I joined the CRADLE trial in July 2015 shortly after funding was awarded and the outline protocol was drafted. I was responsible for undertaking all research management from this point onwards, including achieving ethics approval in the UK and coordinating all approvals in the trial sites. Specifically, I undertook the following work as the research coordinator for the trial presented in this thesis:

- Design of all quantitative and qualitative data collection tools used in this trial
- Co-created the intervention by leading the design of the educational package and implementation strategy
- Undertook the analysis of the feasibility study and led the refinement of the main trial protocol
- Designed all process evaluation measures and created the logic model
- Led the implementation of the intervention and undertook all field work with the help of local site primary investigators and research assistants.
- Co-ordinated quantitative and qualitative data collection and checked all data for quality and completeness with the assistance of a research assistant.
- Analysed all qualitative data and quantitative process outcomes.
- Contributed to quantitative analysis of health outcomes which was led by statistician Paul Seed.
- Contributed to the publication of the trial protocol.
- Drafted the four research papers presented and revised them based on feedback from co-authors.

1 Introduction

1.1 Aim and Chapter Outline

The aim of this thesis is to evaluate the impact of a novel vital sign triage device and educational package on maternal mortality and morbidity in low and middle-income countries. The intervention was implemented as a pragmatic, stepped-wedge cluster randomised controlled trial with a simultaneous process evaluation. Data was used to evaluate the effectiveness and implementation of the intervention.

Chapter one provides an outline of this thesis, explores the quality and availability of existing literature on the epidemiology and aetiology of maternal and neonatal mortality, with a focus on the countries included in the CRADLE trial. The current evidence of interventions aiming to improve early detection of pregnancy complications in maternity care in low-resourced settings will be critically examined. The methodology of evaluating complex interventions in low-resourced settings will be explored, followed by a statement of the problem and the rationale for the research. The research question and hypotheses are described.

The subsequent chapters are based around the published manuscripts resulting from the trial. Chapter two is the published manuscript of the six-month pilot phase before the main trial. This included development of the training materials and exploration of the logic model followed by mixed-method evaluation of implementation in three representative non-trial sites and collection of pilot data in the ten trial clusters, to inform the main trial. Chapter three is the manuscript containing the main trial results. Chapter four is the results of the process evaluation, including qualitative findings and the implications of these on the results for each cluster. Chapter five is a planned sub-group analysis of the women with hypertensive disorders of pregnancy assessing incidence and outcomes of

women, particularly with eclampsia. Key findings in the context of current knowledge, strengths and limitations of the study design, data collection, statistical analysis and intervention implementation, will be explored in Chapter six. The broader meaning of the results and unanswered questions for further research will be identified.

1.2 Epidemiology of Maternal and Neonatal Mortality

The aim of the CRADLE intervention described in this trial was to reduce maternal mortality and maternal morbidity. It is therefore vital to understand the epidemiology of maternal mortality and recent trends in the settings described. The intervention may also impact neonatal mortality and therefore this will be evaluated in the subset of mothers that experienced severe morbidity and mortality. The epidemiology of neonatal mortality is also presented. Through this, we can demonstrate where this intervention fits within the background of international efforts and assess the validity and generalisability of results.

1.2.1 Definitions and Classification

Maternal Death

It is widely recognised that maternal deaths must be counted and described in order to target interventions to improve maternal health. This requires accurate measures of maternal mortality that are comparable internationally. The definition of maternal death is clear (although some uncertainty around the timeframe has existed, historically), but it is not always used or reported uniformly. A systematic review undertaken in 2004 by the World Health Organisation (WHO), identified that only half of the 500 studies included reported their definition of maternal death.(Gülmezoglu et al., 2004) This ambiguity complicates subsequent interpretation of results and it is therefore important that all studies report the definition of maternal death used.

The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) (2010) define maternal death as:

> "The death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes."(World Health Organisation, 2010)

Where cause of death has not been recorded, 'pregnancy related death' can be reported. This is a temporal measure of all deaths that occurred in pregnancy and up to 42 days after delivery, irrespective of cause.(World Health Organisation, 2010) A further category of late maternal death, occurring more than 42 days but less than one year after termination of pregnancy exists.(World Health Organisation, 2010) This is useful for national and analytical purposes as there are limited clinical reasons for the 42-day period. However, the WHO recommends that international reporting of maternal mortality should only include those maternal deaths occurring within the 42-day reference period. It is important for research to clearly define the duration of follow up to ensure that results are comparable across other studies.

The ICD specify that rates of maternal mortality should always specify the numerator as well as the denominator. The denominator should be either the number of live births or the number of total births.(World Health Organisation, 2010) The most common way to report maternal deaths internationally is as a maternal mortality ratio (MMR), which is defined as the number of maternal deaths per 100,000 live births. This enables comparison of risk between countries as seen in the Millennium Development Goals (MDG).(World Health Organisation, 2015b) However, MMR does not account for the fact that women face this risk with each birth and therefore 'Lifetime Risk' is also commonly presented. This is defined as the proportion of women reaching reproductive age who would die of maternal causes;(World Health Organisation, 2007) this gives a useful measure of the burden of disease between countries but is less commonly used in research due to the requirement for accurate population and incidence data.

Neonatal Death

Neonatal death is defined as the death of a live born infant irrespective of the duration of the pregnancy.(World Health Organisation, 2010) This can be classified as an early neonatal death, occurring in the first seven days of life (0-6 days), or a late neonatal death, occurring after the seventh day but before 28 days of life (7-27 days).(World Health Organisation, 2010) Since neonatal death is not correlated with cause of death, it is used more uniformly across the literature compared to maternal death definitions. However, greater accuracy is required in the timing of death to avoid underreporting neonatal deaths as stillbirths.

1.2.2 Errors in Reporting

Despite these standardized definitions, there are methodological challenges in estimating the prevalence of maternal mortality globally. Many countries with the highest rates of maternal mortality lack the comprehensive systems such as civil registration to accurately capture all maternal deaths. Therefore, underreporting continues to pose a major challenge. Additionally, pregnancy status may be unknown, not disclosed or not recorded and therefore the death would not be recorded as a maternal death. Classification of the cause of death is also challenging, especially where certification of death is not formalised.(World Health Organisation, 2007) Despite advances in data collection, a 2015 report from the WHO cited that the use of diverse sources including household surveys, censuses and verbal autopsies limits comparisons of maternal mortality worldwide.(World Health Organisation, 2015b) However, even when a civil registration system exists, in the absence of active case finding, maternal deaths may be misclassified. International comparisons are therefore usually based on estimates of MMR calculated from multiple sources and adjusted to account for the quality of data and degree of uncertainty.(World Health Organisation, 2015b) It is therefore important

that research that involves maternal mortality carefully considers and discloses all methods of counting maternal mortality.

1.2.3 Epidemiology of Maternal Mortality

The overall MMR for the world is 216 per 100,000 live births which equates to 303,000 maternal deaths in 2015. (World Health Organisation, 2015b) Low and middle-income countries (LMIC) account for approximately 99% of these maternal deaths, with 66% from sub-Saharan Arica alone (201,000) and 22% from southern Asia (66,000).(World Health Organisation, 2015b) This means that there are staggering inequalities in rates of maternal death worldwide as shown in Figure 1, where MMR across the world are shown.(World Health Organisation, 2015b) The lifetime risk of maternal mortality in sub-Saharan Africa is 1 in 36, compared to 1 in 210 in southern Asia and 1 in 4900 in high-resource countries.(World Health Organisation, 2015b) Research aiming to prevent maternal mortality must be undertaken in the areas with the highest burden to have the biggest impact.

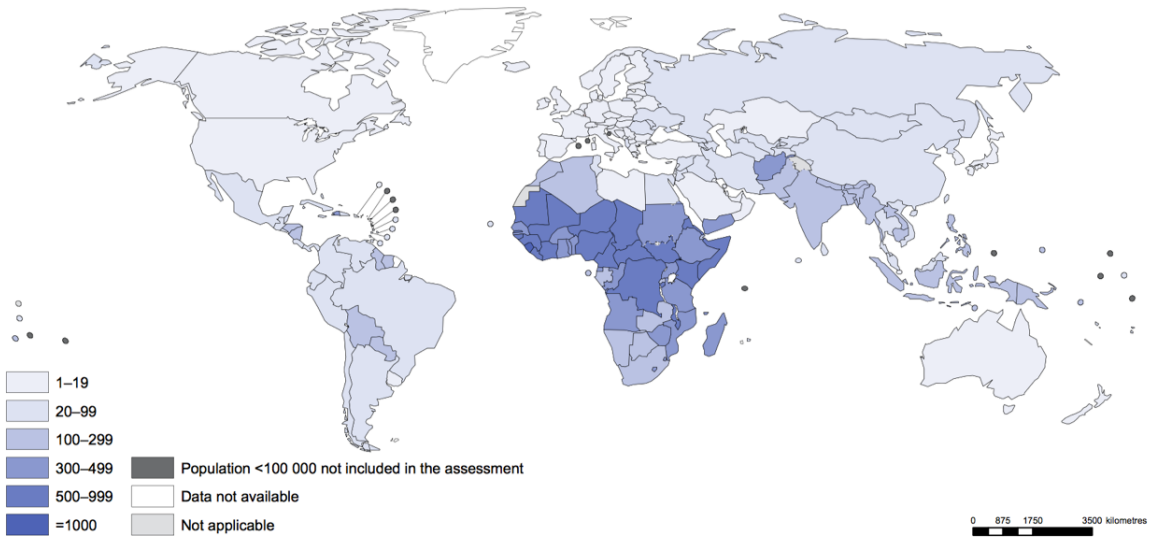


Figure 1 Maternal Mortality Ratio in 2015 (World Health Organisation, 2015b)

The CRADLE Trial (described in this thesis) was undertaken in seven low-income countries (LIC): Sierra Leone, Ethiopia, Malawi, Zimbabwe, Zambia, Uganda, Haiti and India, a middle-income country. Sierra Leone is estimated to have the highest MMR in

the world with 1360 deaths per 100,000 live births in 2015.(World Health Organisation, 2015b) Table 1 on Page 21 shows the MMR in 2015 for all eight countries that participated in the trial. None of these countries have usable vital registration data.(World Health Organisation, 2015b) Therefore, in the absence of accurate data, the range of uncertainty is presented, which is determined by the quality of data used to inform the estimates. The wide range for some countries, such as Zimbabwe, indicate that the MMR could be as low as 363 or as high as 5663 per 100 000 live births therefore estimates should be viewed in context.

Table 1 Maternal Mortality Ratio, number of maternal deaths and lifetime risk of maternal death in the eight CRADLE Trial Countries in 2015 (World Health Organisation, 2015b)

Country	**MMR[a]**	**Range of MMR uncertainty (UI 80%)**		**Number of maternal deaths[b]**	**Lifetime risk of maternal death[c]: 1 in**
		Lower Estimate	Upper estimate		
Ethiopia	353	247	567	11000	64
Haiti	359	236	601	950	90
India	174	139	217	45000	220
Malawi	634	422	1080	4200	29
Sierra Leone	1360	999	1980	3100	17
Uganda	343	247	493	5700	47
Zambia	224	274	582	1400	79
Zimbabwe	443	363	5663	2400	52

[a]MMR estimates have been rounded according to the following scheme: <100 rounded to nearest 1; 100-999 rounded to nearest 1; and ≥ 1000 rounded to nearest 100.

[b]Numbers of maternal deaths have been rounded according to the following scheme: <100 rounded to nearest 1; 100-999 rounded to nearest 1; 1000-9999 rounded to nearest 100 and ≥ 10 000 rounded to nearest 1000.

[c]Lifetime risk has been rounded according to the following scheme: <100 rounded to nearest 1; 100-999 rounded to nearest 10; and ≥ 1000 rounded to nearest 100.

There is also staggering variation in MMR within countries. Data from the 2000 and 2010 censuses on population and housing in Zambia identified that the pregnancy related mortality ratio (as defined above, i.e. similar to MMR but when cause of death is not known and therefore cannot be attributed to pregnancy) is substantially higher in rural areas compared to urban areas when adjusted to account for the number of deaths and births (960/100,000 live births compared to 470/100 000 respectively).(Banda et al., 2015) This is true across sub-Saharan Africa as shown by Figure 2, where despite the wide confidence intervals, suggesting heterogeneous data, there is a clear trend demonstrated.(Ronsmans and Graham, 2006) The pooled estimate for MMR in urban areas is 447/100 000 (95% CI 394-517) compared to 640/100 000 in rural areas in the presented countries (95% CI 590-693). (Ronsmans and Graham, 2006) This is likely due to access to appropriate health services, where globally it is estimated that only 56% of births in rural areas are attended by skilled health personnel compared to 87% in urban areas;(United Nations, 2015) in addition to varying quality of care.(Ng'anjo Phiri et al., 2016) This is in combination with the impact of other wider determinants of health such as higher poverty and lower literacy levels in rural areas as explored in Section 1.3.4. It is therefore important that research into maternal mortality considers the geographical location of study and the potential impact of this on the success of interventions.

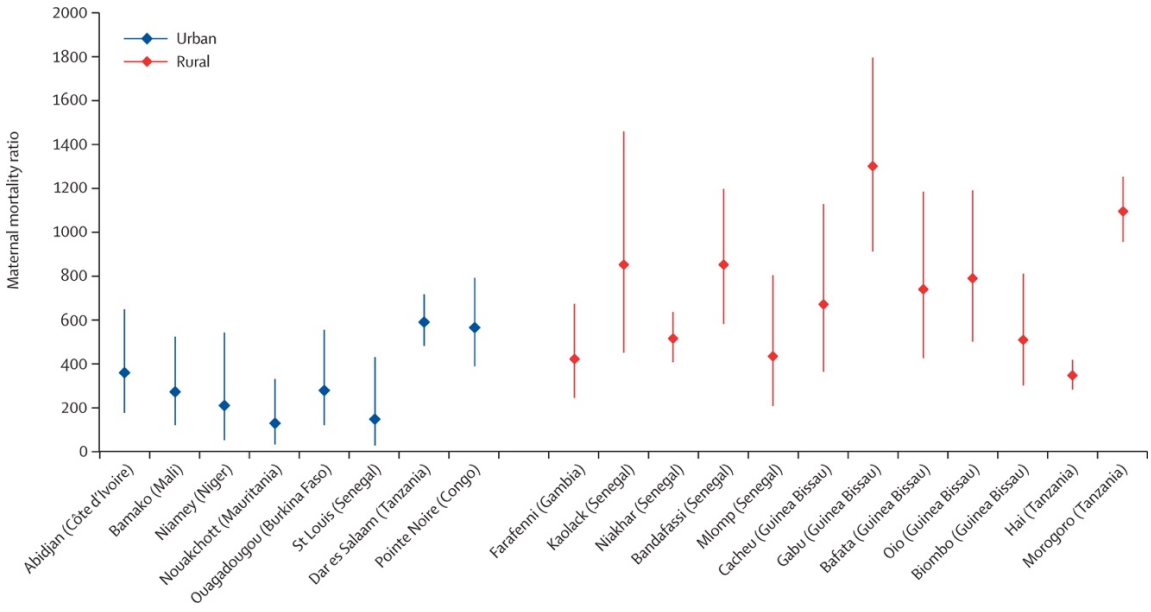


Figure 2 Maternal mortality ratios in urban and rural sites in sub-Saharan Africa (Ronsmans and Graham, 2006)

The majority of maternal deaths in LMIC occur in hospital (but this varies from 40% in Vietnam to 92% in South Africa). The proportion varies greatly depending on country and likely the method of data collection, where capturing deaths in the community can be challenging.(Ronsmans and Graham, 2006) Data are available from a review that identified 14 studies from nine countries and primarily included few deaths from a specific region, and therefore may not be representative of national levels across different countries. Other studies include sisterhood reporting methodology, where households in a predefined geographical area are surveyed about deaths of sisters; this is reliant on accurate recall and knowledge of pregnancy status and only advised for baseline estimates of mortality where no other sources are available.(World Health Organisation, 1997) It was concluded that 71.5% of 1139 maternal deaths in Nigeria occurred in a facility.(Adegoke et al., 2013) There is limited evidence describing the reason for place of death. A 2014 systematic review of the impact of place of delivery in sub-Saharan Africa concluded from three small, population-based cohort studies with a total of 156 deaths, that risk of maternal mortality was significantly increased for facility-based deliveries compared to home deliveries (OR 2.29, 95% CI 1.58-3.31).(Chinkhumba et

al., 2014) It was acknowledged that higher risk pregnancies are more likely to deliver in facilities and therefore this may represent an effective referral system, but it is likely also to be impacted by challenges in providing effective care due to lack of resources to diagnose and treat obstetric emergencies. The lack of reliable country-specific data is important in research and policy, as it is not clear where interventions should target to have the greatest impact on mortality. Therefore, studies reporting maternal mortality should ensure that both rates of hospital and community mortality are accurately presented.

Modelled data, informed by a systematic review of 142 studies and vital registration data, estimates that in 2013 nearly a quarter of all maternal deaths globally occur antepartum (24.6%), a quarter intrapartum or within 24 hours of delivery (27.7%), a third within 42 days of delivery (35.6%) and a minority occur later than 42 days.(Kassebaum et al., 2013) Data from demographic household surveys collected from 84 countries, but over a wide period of time, during which medical practices have changed significantly (1990-2014), found that most deaths occurred in the antepartum and postnatal period but this varied widely in different countries. For example, the rate of antepartum death in Lesotho was 25% compared to 65% in Malawi.(Merdad and Ali, 2018) Demographic Household Surveys are often the most accurate available country specific data but they are reliant on women reporting all their pregnancies in the subsequent three years in addition to the pregnancies of their siblings. Therefore, omission of deaths from abortion and inclusion of incidental deaths are likely. Overall, there are insufficient reliable data to suggest that interventions should target a specific time of pregnancy to reduce mortality. Interventions that can be effective across antenatal care, intrapartum and the immediate post-partum period are required.

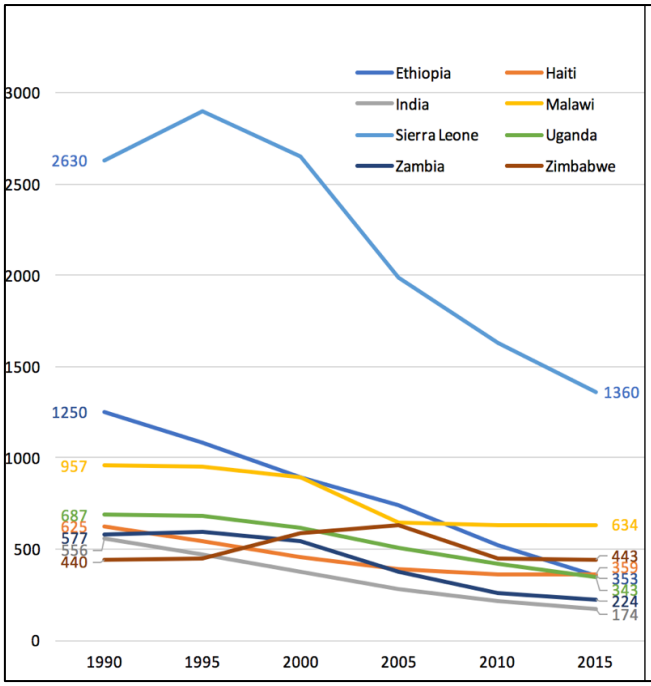
1.2.4 Temporal Trends in Maternal Mortality

Maternal health has been high on the international development agenda since the 1980s with the launch of the Safe Motherhood Initiative in 1987.(Rosenfield and Maine, 1985) The optimistic goal set was to reduce maternal mortality by 50% by 2000.(Starrs, 1997) The main priorities adopted by the international community were antenatal care and screening for high-risk pregnancies, and training of traditional birth attendants to improve the quality of community deliveries.(Starrs, 2006) In 1997, a review of the first decade was undertaken and it was acknowledged that maternal death rates were not declining; in fact, better data collection led to some higher estimates of maternal mortality than previously. (Starrs, 1997, Kassebaum et al., 2013) This was attributed to poorly defined priorities and lack of focused, realistic strategies. (Starrs, 1997, Kassebaum et al., 2013) Nonetheless safe motherhood had become an international priority and consensus was achieved on many effective strategies.

The enormity of maternal mortality worldwide was reinforced with the launch of the MDG in 2000. The aim of MDG 5 was to reduce maternal mortality by 75% within 15 years.(World Health Organisation, 2005a) Substantial improvements were seen with a 45% reduction in the number of maternal deaths worldwide between 1990 and 2015 (from 380/100 000 live births in 1990 to 210/100 000 live births in 2015).(World Health Organisation, 2015b) The target was an annual reduction in the MMR of 5.5% in every country. The actual reduction achieved was 2.6% between 1990 to 2013. However, the greatest reduction was seen in more recent years with the number of maternal deaths in 2010 nearly half that recorded in 2005 and 1990.(World Health Organisation, 2015b).This represents an increase in the annual rate of reduction from 1.1% between 1990-2000 to 4.1% between 2001-2010.

Sustained improvements were demonstrated by many geographical areas with the highest MMR. Southern Asia achieved a 64% reduction in MMR whilst sub-Saharan

Africa showed 49%.(United Nations, 2015) Figure 3 shows how the MMR changed between 1990 and 2015 in the CRADLE trial countries.(World Health Organisation, 2015b) The variation in achievement is notable between countries. Ethiopia and India were close to achieving the target reduction of 75% whereas Zimbabwe saw very minimal change during this time. It is important to understand the existing trends in maternal mortality in individual countries, not only to appreciate the environment within which a new intervention is anticipated to work, and the political climate, but also to understand the potential impact of temporal trends on outcomes during longitudinal data collection.



Country	% Change in MMR between 1990 and 2015[b]	Average annual % change in MMR between 1990 and 2015
Ethiopia	71.8	5.0
Haiti	42.6	3.8
India	68.7	4.6
Malawi	33.8	3.3
Sierra Leone	48.3	4.0
Uganda	50.1	4.1
Zambia	61.2	5.2
Zimbabwe	-0.7	0.9

Figure 3 Trends in estimates of MMR by country in the CRADLE Trial 1990-2015 (World Health Organisation, 2015b)

Despite dramatic advances globally, the MDG were not met and therefore, maternal health remains an important feature of the 2030 Agenda for Sustainable Development. Sustainable Development Goal (SDG) 3 includes a target reduction in the global MMR to fewer than 70 per 100 000 births by 2030, with no country having a MMR of more than twice the global average (140 per 100,000 live births in 2030).(United Nations General Assembly, 2015) This global target accounts for the fact that countries with the highest MMR need to reduce their MMR the most.

The differing contexts and background risk mean that it is impossible to determine exactly which strategies are likely to be most effective at reducing MMR. The WHO has identified five key objectives that are likely to be most useful based on the countries that made good progress towards achieving MDG5.(World Health Organisation, 2015a) The five objectives to achieve SDG3 are:(World Health Organisation, 2015a)

1. Addressing inequities in access to and quality of sexual, reproductive, maternal and newborn health care.
2. Ensuring universal health coverage for comprehensive sexual, reproductive, maternal and newborn health care.
3. Addressing all causes of maternal mortality, reproductive and maternal morbidities and related disabilities.
4. Strengthening health systems to respond to the needs and priorities of women and girls.
5. Ensuring accountability to improve quality of care and equity.

Evidence based interventions that work within these strategies are discussed further in Section 1.3. Research aiming to improve maternal mortality should consider how interventions fit within these broader goals.

1.2.5 Neonatal Mortality

Data from United Nations Children's Fund (UNICEF), WHO, The World Bank Group and United Nations Population Division estimated that in 2016, 2.6 million children died in the first month of life worldwide, approximately 7000 every day.(United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), 2017) This represents nearly half of all under-five deaths internationally. The highest risk is in the first week of life with approximately 38% occurring on the first day.(United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), 2017) The target of MDG4 was to reduce under-five mortality by two-thirds by 2015.(United Nations, 2015) Dramatic improvements were

seen with global rates of neonatal mortality falling from 37 per 1000 live births in 1990 to 19 per 1000 lives births in 2016. However, the rate of decline varied across regions being lower in sub-Saharan Africa at 40% compared to 52% reduction in Southern Asia and 71% in Eastern and South-Eastern Asia.(United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), 2017) The majority of newborn deaths are a result of preterm birth complications, asphyxia or intrapartum complications and infections, together these contribute 74% of all neonatal deaths.(United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), 2017) Many of these deaths could be prevented with simple, cost-effective interventions to address the needs of women and newborns. The new SDG target is to end preventable deaths of newborns and children under five by 2030 with no country having a rate higher than 12 neonatal deaths per 1000 live births.(United Nations General Assembly, 2015) As this thesis primarily addresses maternal mortality and morbidity, with the impact on perinatal mortality a secondary outcome, lack of space precludes further detailed discussion of this issue.

1.2.6 Causes of Maternal mortality

Understanding the aetiology of maternal deaths is vital in designing and targeting interventions to reduce maternal mortality. Maternal deaths can be subdivided into direct and indirect obstetric deaths. Direct obstetric deaths are those resulting from obstetric complications of the pregnant state, from interventions, omissions or incorrect treatment. Indirect obstetric deaths are those resulting from previous existing disease or disease that developed during pregnancy.(World Health Organisation, 2010) Despite these clear categories, reporting on cause of death is variable when there are limited diagnostic resources or uptake of healthcare services. Even when physicians certify death, methods of classifying the cause of death vary internationally, despite guidance from WHO.(World Health Organisation, 2012a) For example, a maternal death from hypovolaemic shock as a consequence of post-partum haemorrhage (PPH) may be exacerbated by underlying pre-eclampsia, with associated coagulopathy. All of these should be

documented but in practice only one or two of them may be written. This was demonstrated by a review of 86 maternal deaths in Malawi, where there was poor correlation between the cause of death attributed by the health care providers (HCP), compared to an expert team trained to use ICD-Maternal Mortality classifications.(Mgawadere et al., 2016) To simplify classification and foster international comparisons the WHO have defined nine groups of causes of death that are clinically relevant, mutually exclusive and inclusive of all causes. These are shown in Figure 4. Understanding the distribution of the relative causes of maternal death is essential to inform the development of interventions to tackle these problems and how maternal death should be measured in future research.

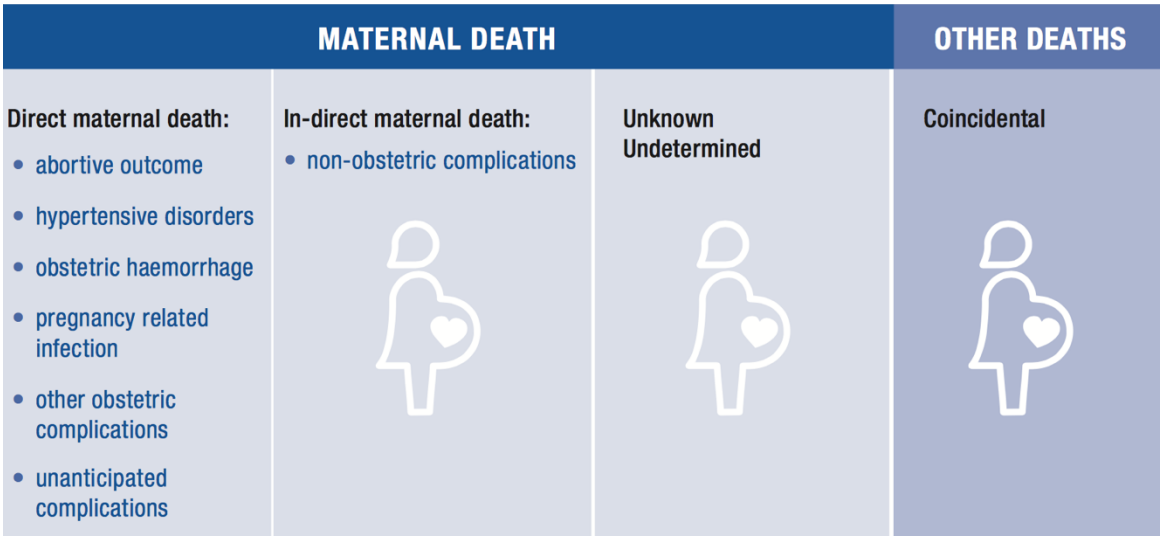


Figure 4 Groups of causes of death during pregnancy, childbirth and the puerperium (World Health Organisation, 2012a)

It is estimated that globally 72% of maternal deaths are due to direct causes and 28% are due to indirect causes.(Say et al., 2014) Haemorrhage is the leading direct cause of maternal mortality worldwide (27%), followed by hypertensive disorders (14%) and sepsis (11%) as shown in Figure 5 on page 32. Together these account for 52% of all maternal deaths worldwide so an intervention aimed at reducing mortality from these causes has maximal potential. The other most common causes of direct maternal death

are abortion (7.9%), embolism (3.2%), complications of delivery (not defined) (2.8%) and obstructed labour (2.8%).(Say et al., 2014)

These figures are modelled from the best available sources (vital registration data (79 countries) and government reports (further 32 countries)) and is informed by 62 378 maternal deaths, however this represents only 2.5% of all maternal deaths during the period analysed (2003-2009). Verbal autopsies informed 26 datasets which are liable to misclassification, especially in cases of death due to abortion, which in many countries is illegal or associated with religious and cultural perceptions leading to it not being disclosed or reported. Abortion may also result in sepsis or haemorrhage and be classified as such; therefore, the underlying cause not be identified. This may have resulted in the lower estimate of 7.9% of deaths resulting from abortion in this study compared to previous global estimates of 13% based on systematic review of research studies.(Khan et al., 2006) Additionally, obstructed labour may result in uterine rupture, haemorrhage or sepsis and is therefore is hard to measure as it is not a mutually exclusive cause. The WHO advise that obstructed labour should only be diagnosed in combination with additional detail, but in practice adherence to this varies between countries.(World Health Organisation, 2012a) Therefore, it can be hard to infer which interventions would have been required to prevent these deaths.

More than a quarter of maternal deaths worldwide are a result of indirect causes (28%) and more than 70% of these are a result of pre-existing conditions including Human Immunodeficiency Virus (HIV) (73.7%).(Say et al., 2014) Indirect maternal deaths are even harder to accurately capture in LMIC due to poor diagnostic capacity, under-reporting and misclassification. For example, death in a woman with HIV infection may be from obstetric causes such as haemorrhage and unrelated to their HIV status, or from an obstetric cause that was aggravated by HIV infection such as sepsis, or from fatal complications of HIV regardless of pregnancy. This is of importance when planning

research studies aiming to accurately capture all maternal deaths in a population, although interventions aiming to reduce mortality from haemorrhage and sepsis are likely to still be of importance in this group.

The most prevalent causes of maternal death also vary by region and despite comparison being limited by use of different methods of modelling, this variation has been consistently reported over the last decade.(Khan et al., 2006, Say et al., 2014) Haemorrhage is the most common cause of maternal death in sub-Saharan Africa (24.5%) and Southern Asia (Figure 5) (30.3%) but in high-income countries (HIC), it represents only 16.3% of maternal deaths. Hypertensive disorders are of greater importance in Latin America and the Caribbean contributing 22.1% of all maternal deaths compared to 16.0% in sub-Saharan Africa and 10.3% in Southern Asia.(Say et al., 2014) Deaths from sepsis are most prevalent in Southern Asia (13.7%) compared to 10.3% in sub-Saharan Africa and 4.7% in HIC. The reason for these differences are multifactorial but given that all causes are consistently lower in HIC, preventing mortality with timely delivery of effective interventions is possible. In order to reduce mortality and morbidity in pregnancy, research needs to target the most common causes and ensure it builds upon existing understanding of effective interventions. Therefore, the prevalence, aetiology and management of the three leading causes of maternal death are explored in the subsequent section.

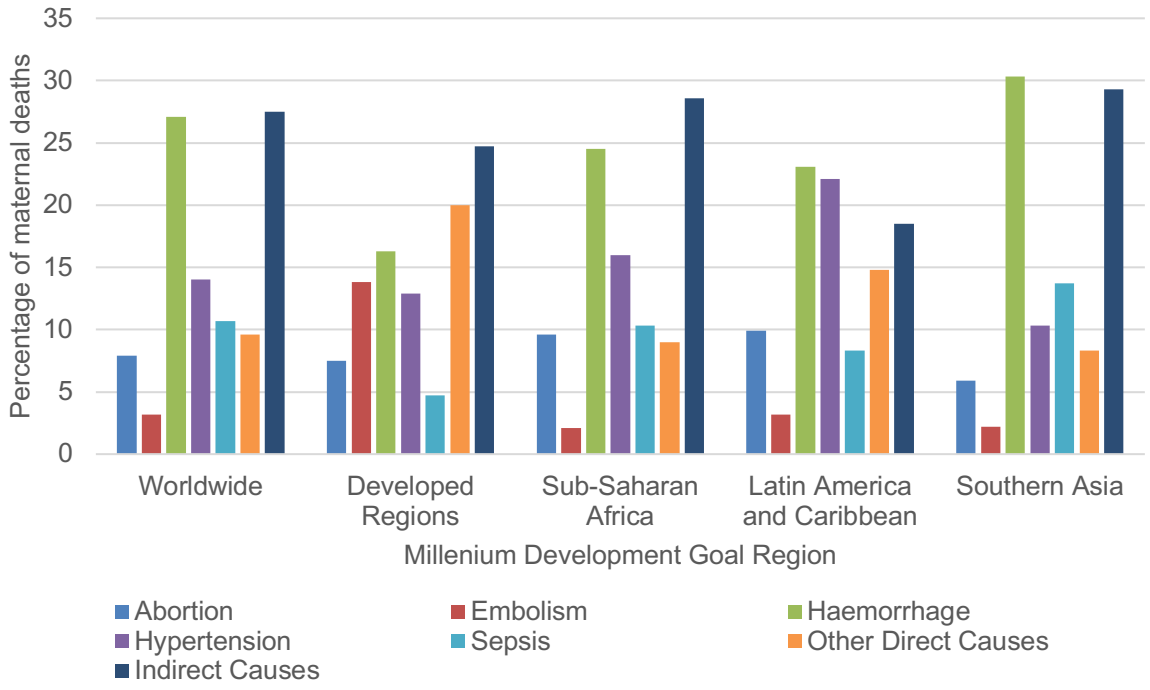


Figure 5 Distribution of causes of death by MDG region included in the CRADLE Trial (Say et al., 2014)

1.3 Understanding the leading causes of maternal mortality

1.3.1 Haemorrhage in Pregnancy

PPH is the most common form of obstetric haemorrhage, defined as blood loss of 500ml or more within 24 hours of birth.(World Health Organisation, 2012b) A systematic review of 123 datasets demonstrated that globally 10.8% of women suffer from PPH (95% CI: 9.6-12.1%). However, this prevalence varied widely across regions from 7.2% (95% CI: 6.3-8.1%) in Oceania to 25.7% (95% CI: 13.9-39.7%) in Africa. Severe PPH (>1000ml), which is associated with substantial morbidity, is much less common with a global prevalence of 2.8% (95% CI: 2.4-3.2%). But again, the prevalence is almost doubled in Africa (5.1%; 95% CI 0.3-15.3%).(Calvert et al., 2012) These prevalence's are higher than previous observational studies such as the WHO Multi Country Study where case note reviews of 314,623 facility births in 29 countries found an overall prevalence of severe PPH of 1.2%.(Sheldon et al., 2014) This difference between findings may be a result of different study populations or standard of care, as the WHO study only included

facilities that could provide caesarean deliveries, and in which 92.7% of the population received prophylactic uterotonics. This is not likely to be representative of those that delivered in lower level facilities or in the community, where prevalence of PPH may be higher. Additionally, this study included visual assessment of PPH and relied on documentation by HCP, whereas the majority of research studies include measured blood loss.(Sheldon et al., 2014) It is well reported that visual estimation underestimates blood loss by an average of 100-150mls and substantially underestimates blood loss of >500ml (by 30-50%).(Prasertcharoensuk et al., 2000, Patel et al., 2006, Hancock et al., 2015) Estimates of the prevalence of PPH, a common event, may therefore be conservative.

Despite its limitations, the WHO Multi Country study provides the best available evidence of the case fatality from PPH. It reports that 3.1% of PPH events resulted in maternal death,(Sheldon et al., 2014) translating to an estimated 82,000 maternal deaths worldwide each year.(Say et al., 2014) Nearly all of these deaths occur in LMIC regions, with Sub-Saharan Africa contributing 48.5%.(Say et al., 2014) This considerable inequality is evident when comparing the rate of maternal death from PPH in the UK, which is 0.88 per 100,000 births,(Knight M, 2017) compared to approximately 150 per 100,000 in sub-Saharan Africa.(Weeks, 2015) Severe maternal morbidity (17.6%) as a result of PPH, such as anaemia, disseminated intravascular coagulation, blood transfusion, hysterectomy or renal failure, impacts many more women.(Sheldon et al., 2014)

The risk of fatality or severe morbidity from PPH is undoubtedly dependent on clinical management such as administration of uterotonics and requirement for referral from another facility.(Sheldon et al., 2014) However, there are also individual variables which significantly affect the incidence of severe morbidity, such as age, parity, and anaemia. These likely also contribute to overall differences in risk between countries.(Sheldon et

al., 2014) For example, whilst there is limited evidence to support an increased risk of mortality, data from the WHO Multi Country study demonstrated that 38.7% (n=228) of women that experienced severe morbidity as a result of PPH had pre-existing anaemia compared to 14.7% (n=405) of those that didn't ($p<0.0001$).(Sheldon et al., 2014) This is supported by evidence from a retrospective cohort study where the risk of PPH in women with severe anaemia (<7g/dL) was increased 9-fold (aOR 9.45, 95% CI 2.62 to 34.05).(Nair et al., 2016) In countries like India, where the prevalence of anaemia is reported to be as high as 70-80%, this is likely to contribute to increased morbidity and mortality from PPH.(Toteja et al., 2006)

The most common cause of PPH is uterine atony. The uterus is composed of interlacing muscle fibres, but failure of the myometrium to contract following delivery allows blood to continue to flow at a rate of 500ml/minute to the placental tissue. Therefore, blood loss can be rapid. Other causes are retained placental tissue, tears to the uterus, cervix or vagina and disorders in blood clotting. Prospective data from a study of 407 women in Egypt and Nigeria suggests that within an average of 20 minutes from delivery, women can be in hypovolaemic shock secondary to PPH.(Turan et al., 2011) Therefore, it is vital that all facilities undertaking deliveries have appropriate skills and resources to be able to initiate timely treatment and rapid referral.

The WHO makes 32 evidence-based recommendations for the prevention and treatment of PPH.(World Health Organisation, 2012b) It has been concluded that timely delivery of these interventions should prevent the majority of deaths.(Khan et al., 2006) The WHO guideline was published in 2012 and recommends intravenous oxytocin, a uterotonic, as the single first line treatment for PPH.(World Health Organisation, 2012b) However, more recently, a Cochrane review of 140 randomised trials, including 88,947 women, concluded that the most effective options at reducing PPH >1000ml were ergometrine with oxytocin (Risk ratio (RR) 0.77; 95% CI 0.61-0.95) compared to oxytocin

alone.(Gallos et al., 2018) However, oxytocin requires storage at between 2-8^{o}C and therefore its efficacy in low-resource settings ,where electricity supply can be intermittent, is likely to be reduced. A systematic review, including 559 oxytocin samples from clinical practice, found that nearly 50% failed quality testing due to insufficient amounts of active ingredient.(Torloni et al., 2016) Most recently, a large randomised controlled trial (RCT) undertaken in 10 countries individually randomised 29,645 women and demonstrated that heat-stable carbetocin is as effective as oxytocin at preventing PPH >500ml and >1000ml (RR 1.01; 95% 0.95-1.06 and 1.04; 0.87-1.25 respectively).(Widmer et al., 2018) No uterotonic drugs have been shown to make a meaningful difference in preventing maternal deaths or severe morbidity as outcomes are relatively rare. However, evidence from a recent RCT has shown that tranexamic acid, an antifibrinolytic drug, reduces maternal death from PPH, especially when given in the first three hours after delivery.(WOMAN Trial Collaborators, 2017) Second line treatments include oxytocin with prostaglandins such as misoprostol and carbetocin. The evidence for further interventions such as uterine massage, balloon tamponade and uterine artery embolization is of low quality, but these may remain the best options when uterotonic medication has failed.(World Health Organisation, 2012b) Surgical management with hysterectomy is undertaken as a last resort when other available conservative interventions have failed.(World Health Organisation, 2012b)

Overall, PPH is a common event effecting one in ten women and is a major cause of preventable maternal morbidity and mortality worldwide. There are treatments that work but they require recognition of the haemorrhage and early administration to be effective. In resource poor environments, identifying who is at greatest risk and prioritising early administration of medication and referral could save lives, but current methods to predict risk are inadequate. Estimation of blood loss is not reliable and therefore measurement of vital signs and clinical condition is key. Research that aims to reduce maternal

morbidity and mortality from PPH remains a key priority in achieving the sustainable development goals.

1.3.2 Hypertensive Disorders in Pregnancy

Hypertensive disorders of pregnancy (HDP) encompass chronic hypertension, gestational hypertension (new hypertension without proteinuria), pre-eclampsia and eclampsia. Approximately 10% of women will have elevated blood pressure (BP) during their pregnancy,(Duley, 2009) but the greatest burden of disease is from pre-eclampsia and eclampsia. Pre-eclampsia is defined as new onset hypertension (greater or equal to 140 mmHg systolic or 90 mmHg diastolic) with significant proteinuria or end-organ damage, (such as renal insufficiency, liver involvement, neurological or haematological complications) or uteroplacental dysfunction (such as fetal growth restriction after 20 weeks of gestation).(Brown et al., 2018) The best available data from 78 datasets and nearly 39 million women from 40 countries estimated the prevalence to be 4.6% (95% CI 2.7-8.2%).(Abalos et al., 2013)

The risk of dying from pre-eclampsia in the UK is now one in a million;(Knight M, 2016) whereas in a LIC this is one in 3000,(Say et al., 2014) translating into around 42,000 maternal deaths globally in 2015. The burden of morbidity is even greater, with 8.2% of women developing severe morbidity or “near miss” outcomes, eight times higher than women without pre-eclampsia.(Abalos et al., 2014a) Secondary analysis of the WHO multi country survey concluded that the most common complications of pre-eclampsia in LMIC are coagulation dysfunction (affecting 43%), respiratory dysfunction (25%), cardiovascular dysfunction (24%) and hepatic dysfunction (24%).(Abalos et al., 2014a) Estimates of prevalence and resulting disease burden are challenged by various definitions and methods of confirming diagnosis. Future research should take this into consideration.

Eclampsia is defined as convulsions or coma in a woman with high BP in the absence of known neurological cause. The best estimates of the prevalence of eclampsia globally are between 0.3% (n=875; 95% CI 0.1-0.8%) (Abalos et al., 2014a) and 1.4% (95% CI 0.1-2.9%) of all deliveries.(Abalos et al., 2013) Women under 20 years of age, with low levels of education, in their first pregnancy are all reported to have higher prevalence of eclampsia.(Abalos et al., 2014a) There are limited data reporting the prevalence of maternal deaths related to eclampsia globally. Estimates from 16 datasets of average quality reported the case fatality rate to be 8.3% (Abalos et al., 2013), higher than the 3.7% reported from the WHO multi-country cross-sectional (n=32 maternal deaths).(Abalos et al., 2014a)

Despite its frequency and burden of disease globally, the pathogenesis of pre-eclampsia is only partially understood. Abnormal placentation at the start of pregnancy as a result of gene variants, inflammation, oxidative stress and the renin angiotensin system are all recognised.(Mol et al., 2016) Risk is increased by the presence of factors such as previous hypertension or pre-eclampsia, kidney disease, diabetes, increasing age, primiparity and greater pregnancy intervals.(National Institute for Health and Care Excellence, 2010) Advances in risk prediction of pre-eclampsia is explored in Section 1.4.1 but there are currently no specific screening tests for pre-eclampsia that have sufficient clinical and cost effectiveness to be uniformly adopted into clinical practice.(Hodgkinson et al., 2014)

A systematic review of six articles (n=2573) concluded that symptoms of pre-eclampsia such as headache, epigastric pain and visual disturbance do not adequately predict maternal outcomes (Thangaratinam et al., 2011b) and pre-eclampsia can regularly occur without symptoms. Therefore, BP monitoring remains the most important screening test for diagnosis. Whilst causality cannot be stated from case reviews, evidence from the UK Confidential Enquiry into Maternal and Child Health have highlighted that failure to

accurately measure, understand and act on abnormal BPs in pregnancy in a timely manner results in increased mortality and morbidity.(Cantwell et al., 2011)

The only cure for pre-eclampsia and eclampsia is delivery of the placenta. Evidence from a RCT of 756 women with gestational hypertension or mild pre-eclampsia showed that induction of labour after 36 weeks of pregnancy is effective at preventing maternal morbidity without increasing neonatal morbidity.(Koopmans et al., 2009) Therefore, the WHO recommends that all women with pre-eclampsia at 37 weeks' gestation onwards are delivered.(World Health Organisation, 2011) Prior to 34 weeks' gestation, elective delivery is associated with an increase in neonatal adverse outcomes such as respiratory distress syndrome (RR 2.3; 95% CI 1.39-3.81).(Churchill et al., 2013) Therefore, expectant management is recommended.

There is high quality evidence that antihypertensives are effective at halving the risk of developing severe hypertension in those with mild or moderate HDP (RR 0.49; 95% CI 0.40-0.60; 11 trials, n=638) but this was not associated with any reduction in maternal or neonatal morbidity.(Abalos et al., 2014b) There is also evidence from smaller studies, at greater risk of bias, that treating severe hypertension is effective at reducing BP (RR 0.33, 95% CI 0.15-0.70).(Duley et al., 2013) Again, no reduction in maternal morbidity and mortality was demonstrated but the studies included were all comparing antihypertensives, not placebo and therefore adverse events were likely to be avoided in both groups. There is also evidence that severe hypertension is associated with increased risk of morbidity as explored in Section 1.4.2 and therefore the WHO recommends treating severe hypertension.(World Health Organisation, 2011)

There is also good evidence from a systematic review, including six trials and 11,444 women, that magnesium sulfate more than halves the risk of eclampsia in women with pre-eclampsia compared to placebo or no treatment (RR 0.41; 0.29-0.58).(Duley et al.,

2010) It is considered an essential drug by the WHO.(World Health Organisation, 2017b) However, it has not been shown to significantly reduce maternal death or serious maternal morbidity.(Duley et al., 2010)

The lack of evidence for direct impact on morbidity and mortality for these interventions is likely because studies are generally undertaken in HIC where morbidity is rare and therefore sample sizes to demonstrate such an effect would be prohibitively large. In addition, studies are often confounded by the fact that elevated BP is routinely treated and therefore adverse outcomes are avoided (treatment paradox). Estimating the true effect of interventions in practice is complicated. For example, a systematic review concluded from 10 studies that antenatal screening for hypertension and proteinuria, treatment of pre-eclampsia and eclampsia with magnesium sulfate and early delivery could reduce mortality by 84-99%,(Ronsmans and Campbell, 2011) but the studies had heterogeneous methodology, precluding definitive conclusions.

In conclusion, HDP affect one in ten pregnancies and are the second leading cause of maternal morbidity and mortality worldwide.(Say et al., 2014) There are effective interventions to treat pre-eclampsia and prevent eclampsia, but they require regular, accurate measurement of BP throughout pregnancy to ensure that early diagnosis can be made and timely management can be delivered. Effective management can prevent the majority of adverse outcomes from HDP.(Campbell and Graham, 2006)

1.3.3 Sepsis in Pregnancy

Sepsis consists of three components: infection, host response to infection and organ dysfunction. The definition of sepsis has only recently been agreed.(World Health Organisation, 2017a) In 2017 a systematic overview, which considered all reviews of maternal sepsis, articles on the criteria for sepsis and current guidelines (26 studies, nine guidelines and three WHO documents), concluded that a variety of definitions of

maternal sepsis, terms and criteria for diagnosis were currently in use.(Bonet et al., 2017) As a result, 48 experts led by the WHO created a new consensus definition: “a life-threatening condition with organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or post-partum period”.(World Health Organisation, 2017a)

The previous lack of clear definition and criteria for diagnosis means that estimating the prevalence of sepsis globally is difficult. Most data are from studies undertaken in hospitals and are therefore not likely to reflect population levels or fully capture sepsis occurring in the postpartum period, which is thought to be common. Data from HIC suggest an incidence of maternal sepsis of 9 to 49 per 100,000 deliveries per year.(Oud, 2014) However, even in HIC the six studies included in this review have variable quality, with small samples (Waterstone et al., 2001, Acosta et al., 2012, Mabie et al., 1997), absent definitions of sepsis (Kramer et al., 2009) or inclusion of non-standard eligibility criteria (Acosta et al., 2013). Drawing conclusions on the current prevalence of maternal sepsis in LIC is challenging due to the scarcity of reliable data.(van Dillen et al., 2010) Publication of a large prospective cohort study across all WHO regions is awaited.(Bonet et al., 2018)

The burden of disease from maternal sepsis is undoubtedly high, accounting directly for 11% of all maternal deaths, approximately 33,000 women annually,(Say et al., 2014) and likely to contribute towards many more, as a complication from abortion and obstructed labour. Nearly all of these deaths are in LMIC.(Say et al., 2014) This is in contrast to HIC; for example in the UK, between 2013 and 2015 just 24 women died from sepsis.(Knight M, 2017) In addition to causing high numbers of maternal mortality globally, data from a cross sectional case-control study in the UK (n=365 cases of severe sepsis) identified that for every maternal death, 50 women have life-threatening morbidity.(Acosta et al., 2014) In LIC, where delays in diagnosis and treatment are more common, this is likely to be even greater.

The most common causes of puerperal infections include endometritis, chorioamnionitis and pyelonephritis.(van Dillen et al., 2010) Whilst there is limited evidence, it is widely reported that pregnant and peri-partum women are particularly vulnerable to infection due to physiological and immunological changes, particularly during the postpartum period.(Acosta and Knight, 2013, Kourtis et al., 2014) Physiological barriers to infection are disrupted during labour and both caesarean section and operative vaginal delivery are associated with increased risk of infection.(Acosta et al., 2014) This is confounded by additional factors in a low-resource setting, where overcrowding, low socioeconomic status, malnutrition, anaemia and HIV are more common and predispose women to sepsis.(Kramer et al., 2009, van Dillen et al., 2010) The likelihood of developing, and the severity of infections such as influenza, hepatitis and malaria are also greater in pregnancy.(Kourtis et al., 2014) This is potentially due to the increased heart rate (HR), stroke volume and reduced pulmonary capacity in pregnancy, increasing the risk of hypoxaemia. Additionally, these physiological adaptations may mask signs of sepsis, and pregnant women generally compensate well, even in the presence of severe infection. This can result in delays in diagnosis and initiation of treatment which costs lives.(Knight M, 2014)

It is well known that timely recognition is the most crucial step in severe sepsis management.(Gaieski et al., 2010) A variety of diagnostic tools and triggers exist outside of pregnancy,(Singer et al., 2016, Shankar-Hari et al., 2016) which have recently been adapted for maternal sepsis and incorporated into national guidance (Royal College of Obstetricians and Gynaecologists, 2012, NICE, 2016, The UK Sepsis Trust, 2017). They rely on accurate measurement of vital signs in order to trigger the pathways and rapid action. This is explored further in Section 1.4.5.

Evidence demonstrating the effect of sepsis management in pregnancy is scarce and as a result there are no evidence-based recommendations specific to the management of sepsis in pregnancy.(Guinn et al., 2007) As with sepsis in general population,(Dellinger et al., 2013) the key actions involve early resuscitation with administration of oxygen, intravenous antibiotics and fluids within one hour and checking serum lactate. This package of management is known as early goal directed therapy.(Royal College of Obstetricians and Gynaecologists, 2012) There is good evidence from randomised trials and meta-analysis of observational studies (n=434,447 patients) that outside of pregnancy, early goal directed therapy reduces mortality from sepsis.(Damiani et al., 2015, Rivers et al., 2001) There are no large, high-quality studies demonstrating efficacy of this bundle in pregnancy in a high or low-resource settings. The bundle requires basic infrastructure such as water and sanitation and key resources such as fluids, antibiotics and monitoring equipment; its application and effectiveness in LIC remains to be determined.

Evidence to support the use of specific antibiotics is also low quality with the majority of research undertaken in HIC, yet the WHO does recommend specific antibiotics for treatment of chorioamnionitis and endometritis.(World Health Organisation, 2015c) In practice, choice is likely to be dependent on availability and should take into account patient response and culture results. Control of the source of sepsis, such as caesarean delivery, hysterotomy or hysterectomy is key. However, the evidence for this is limited to case reviews of maternal deaths in the UK, which show that delay can be fatal.(Knight M, 2014)

Overall, maternal sepsis is the third most common cause of maternal death globally. Although there is limited evidence in pregnancy, data from outside of pregnancy and review of cases suggest it is largely preventable with early diagnosis and rapid initiation of antibiotics, fluids and source control. However, the severity of illness can be masked

by pregnancy and delays cost lives. Therefore, accurate measurement of vital signs and reliable, easy-to-use tools to facilitate diagnosis and timely management in LMICs is vital.

1.3.4 Wider determinants of maternal mortality

The main clinical causes of maternal death have been identified. However, the underlying factors that contribute are dependent on many broader determinants of health. These include closely interlinked cultural, demographic and socioeconomic factors that all put a woman at higher or lower risk. Individual risk factors include young or old age,(Blanc et al., 2013) nulliparity or grand multiparity and social isolation.(Mbizvo et al., 1993) Wider determinants of poverty, education of the mother and partner and gender inequality are known to contribute.(Say and Raine, 2007)

One way to view these determinants is to consider the levels at which they influence health. The first components are those that directly impact maternal health, for example, haemorrhage and infection. Interventions that target these immediate determinants focus on improving the outcomes for women with these obstetric complications. The second components are the intermediate determinants of maternal health. This includes the health status of women, for example nutritional status and comorbidities such as HIV. It also includes access to services and availability of high-quality care. Interventions that target the intermediate determinants should reduce the likelihood of women experiencing a serious complication during pregnancy. Distant determinants affect the wider society as well as women individually. They can be complex and interrelated, for example education and gender equality. Efforts to reduce maternal mortality by addressing distant determinants may include avoiding unwanted pregnancy.(McCarthy and Maine, 1992)

This simple model describes the levels of determinants but does not explore any of the challenges in this care being received. The ‘three delays’ conceptual framework presents the impact of these determinants on access to care. Whilst these are described as three

distinct delays, they comprehensively cover complex interactions.(Thaddeus and Maine, 1994)

- Delay 1 is in the decision to seek medical care; this may be due to the cost or distance to the facility, lack of knowledge about necessity for care or perceived quality of care.
- Delay 2 is in reaching an appropriate facility; this may include physical accessibility factors such as availability or cost of transportation.
- Delay 3 is in receiving adequate care when a facility is reached; this may include shortages of equipment or medical supplies or trained staff.

This framework has been criticised for focussing primarily on factors that affect the time taken from the onset of a complication and its outcome. This implies that action usually occurs only in response to an emergency and involves moving to a facility. Instead it is proposed by Gabrysch et al. that health seeking behaviours are likely to differ for preventative care rather than in response to an emergency.(Gabrysch and Campbell, 2009) They reviewed over 80 studies and two reviews then grouped determinants of health that influence facility delivery into four categories: sociocultural factors, perceived need and benefit of attending, economic and physical accessibility.

The direct action of most health care interventions is on the immediate determinants of health. However, they may also improve intermediate determinants such as the perceived need for care and physical accessibility. Perceived quality of care is dependent on the experiences of women and others they know and only partially correlates with medical quality of care. For example, measurable markers of quality such as waiting times or medical supplies may not be perceived to be as important as other subjective measures such as negative staff attitude, which is frequently reported in qualitative studies to deter women from delivering in facilities.(Gabrysch and Campbell, 2009) Multiple small, single country quantitative studies have looked at staffing levels and availability of equipment in relation to the proportion of facility deliveries (as a surrogate

for perceived quality of care) and found no relationship.(Hounton et al., 2008, Mayhew et al., 2008) Health care interventions may also improve the perceived need or benefit of health care by increasing the availability of information and knowledge regarding pregnancy and its risks. This may be disseminated through antenatal care, which is also associated with increased facility delivery.(Gabrysch and Campbell, 2009) Therefore, research in this field should be aware of the complexity of perceived quality of care and consider the possibility of measuring surrogate markers if this is a key strategy of an intervention.

Healthcare interventions aimed at the community setting may also impact on the physical accessibility of care, a further intermediate determinant of health. The vast majority of quantitative studies report that women living far away from facilities are less likely to have skilled attendance at delivery,(Gabrysch and Campbell, 2009) although this is likely to be confounded by other factors such as poor road infrastructure, poverty and limited access to information. Some studies show varying relationships; for example, two small studies utilising surveys of deliveries concluded that distance was not related to facility delivery rates as the availability of health care services and transport in their region were good.(Duong et al., 2004, Paul and Rumsey, 2002) In comparison, one large study with rigorous observational methodology in Bangladesh, showed that even small distances (1-3km) can be insurmountable irrespective of socioeconomic situation, when there are factors such as floods and cultural barriers to travel.(Chowdhury et al., 2006) As skilled birth attendance at delivery is one of the most successful interventions to reduce maternal mortality, these studies demonstrate the importance of the physical environment on health, which may impact on the success of any intervention. It is therefore vital for research aiming to reduce maternal mortality in LMIC to describe the physical environment so that the context of the trial outcomes can be understood and replicated if successful.

Clinical interventions are unlikely to directly impact the distant determinants of health such as sociocultural factors (marital status, traditional beliefs and women's autonomy to decide to seek health care). Similarly, economic factors such as ability to pay for health care are closely related with access to healthcare and outcomes. However, these may all affect the success of any health care intervention. It may be desirable to identify and measure key wider determinants of health within a trial area in order to understand the context within which an intervention is aiming to create change. In practice, many of these factors are closely interrelated and hard to measure within the constraints of research funding.

1.4 Interventions aiming to reduce maternal morbidity and mortality by early detection of pregnancy complications

Section 1.3 has described the key clinical interventions that are successful in treating the major clinical causes of maternal mortality: PPH, HDP, sepsis. All these interventions are dependent on timely recognition of pregnancy complications in order to save lives. This section therefore reviews the evidence relating to interventions aiming to improve early detection of pregnancy complications.

1.4.1 Risk prediction for early detection of pregnancy complications

The WHO define routine antenatal care as the care provided by HCP to all pregnant women to ensure the best health conditions for pregnancy.(World Health Organisation, 2016) Identification of those at risk in order to prevent and manage pregnancy complications is one of the key components.(Abalos et al., 2016) There is limited evidence demonstrating the success of antenatal care in preventing morbidity and mortality. Hospital case series and confidential enquiries of maternal death often show that higher mortality is associated with lack of antenatal care.(Carroli et al., 2001) These studies lack control groups and therefore cannot be used to establish effectiveness. This

lack of reliable control groups also relates to observational studies. Comparing those who did or did not attend antenatal care, or the timing of attendance, is confounded by socio-economic factors, education, distance from and access to other health services. Equally, women cannot be randomised to no care. Therefore, trials have examined different schedules of care (Dowswell et al., 2015) or processes such as availability of equipment.(Betrán et al., 2018)

One strategy for early detection in antenatal care is to identify those at greatest risk of pregnancy complications so that they can have more monitoring or referral than the usual schedule of care. This was a key strategy in preventing mortality in the safe motherhood campaign discussed in Section 1.2.4.(Rosenfield and Maine, 1985) In order for interventions aiming to reduce morbidity and mortality by detecting risk to be successful, there needs to be:(Carroli et al., 2001)

- A screening programme for the whole population to determine those at risk;
- A means of identifying those at risk of the most important causes of mortality and morbidity;
- An early phase to the condition where it is beneficial to monitor and treat;
- A pathway to ensure that those at increased risk receive referral or management, which requires the ability and motivation of the patient to reach and receive care as well as the motivation and ability of HCP to provide care.

Prediction of pre-eclampsia

In the case of pre-eclampsia, systematic reviews have identified known factors in maternal history and demographics that are strong predictors of risk,(Duckitt and Harrington, 2005, Bartsch et al., 2016) alongside evidence that biochemical markers (Anderson et al., 2012) and uterine artery Doppler's (Velauthar et al., 2013) may also be of benefit. A recent systematic review identified 24 studies combining different combinations of these risk predictors into models. Overall conclusions on effectiveness

were not made due to the overall low-quality methodology, with small sample sizes and insufficient factors included in many models.(Brunelli and Prefumo, 2015) Although some large, multi-centre studies have shown that combining risk factors can predict pre-eclampsia with reasonable reliability (sensitivity and specificity 88% and 80% respectively,(Myatt et al., 2013); Area Under the Curve (AUC) 0.9; 95% CI 0.79-1.0)(Kenny et al., 2014)) as well as its associated adverse maternal outcomes (AUC 0.88; 0.84-0.92),(von Dadelszen et al., 2011) no predictive risk model for pre-eclampsia (beyond screening for clinical risk factors) has been adopted into widespread clinical practice.

These studies use different measures of risk, from symptoms, signs and routine blood results (von Dadelszen et al., 2011) to combinations of biomarkers (Myatt et al., 2013) and both.(Kenny et al., 2014) A recent systematic review compared 22 risk models that include simple factors based on maternal characteristics to 48 'specialised models' that include tests not routinely performed in the general antenatal setting such as uterine artery Doppler. It was concluded from nine studies that specialised models were better predictors of risk,(Al-Rubaie et al., 2016) although these are less likely to be universally available in low-resource settings. Simple models varied in their ability to discriminate between high and low-risk women (AUC 0.67-0.90) and to predict early-onset pre-eclampsia (AUC 0.72 -0.90) and late onset pre-eclampsia (AUC 0.78-0.85). As most models were developed to predict either early or late-onset pre-eclampsia, no simple models have been validated to predict risk of any (early or late) pre-eclampsia, which would be most useful in low resource settings. Additionally no validations were undertaken LIC populations.(Al-Rubaie et al., 2016) Therefore, there is no single model that is currently recommended and suitable for low resource settings.

There is high-quality evidence that starting aspirin in early pregnancy in those at risk can reduce the risk of pre-eclampsia by 17%(OR 0.83; 95% CI 0.77-0.89)(Duley et al., 2007)

and the benefits of early treatment once diagnosed have been previously described. Therefore, risk prediction allows these treatments to be appropriately administered and management optimised to reduce maternal morbidity. However, the disease progression is not always linear. Some women can rapidly develop early onset pre-eclampsia which is associated with increased risk of morbidity.(von Dadelszen et al., 2011) Even if risk prediction and aspirin prophylaxis is undertaken, no model has perfect performance and measurement of BP remains a critical step in early detection of pre-eclampsia.

Prediction of sepsis

Whilst the benefit of predicting pre-eclampsia is clear, there is a limited evidence to support risk prediction in sepsis. The best available evidence from a large, population cohort and a prospective case control study have identified multiple risk factors for maternal sepsis and severe sepsis in HIC (e.g. Black ethnicity, primiparous or multiple birth).(Acosta et al., 2013, Acosta et al., 2014) However, it is not known whether these risk factors are the same in LIC and there is no evidence for combining these factors, or any other measures to predict overall risk.

There is a short period early in the clinical course where initiation of treatment would be beneficial. A national case-control study of 296 cases found that in 89% of severe sepsis cases and 95% of septic shock cases there was less than 48 hours between the first sign of systemic inflammation and diagnosis.(Acosta et al., 2014) This has been recognised by the WHO in a recent statement that two criteria of sepsis should be used, one for early identification to enable prompt treatment and one for confirmed sepsis for epidemiological purpose.(World Health Organisation, 2017a) However, as yet these criteria are not defined and the predictive capacity of abnormal vital signs is low as discussed in Section 1.4.2 below.

Prediction of postpartum haemorrhage

There are several known risk factors for severe PPH. Pre-pregnancy factors include increasing age, high body mass index and previous caesarean.(Cameron, 2012) Pregnancy-acquired risk factors for PPH include multifetal pregnancy, placenta praevia and pre-eclampsia; while intrapartum risk factors include raised maternal temperature, infection and operative delivery.(Cameron, 2012) However, a systematic review found no studies exploring the effectiveness of risk screening in preventing mortality from haemorrhage.(Carroli et al., 2001) Despite the knowledge of these factors, identifying accurately who is at risk and preventing haemorrhage remains a challenge. This is because these factors alone have a low sensitivity to predict haemorrhage and there is limited evidence of their combination in risk models.(Koopmans et al., 2014, Sittiparn and Siwadune, 2017) In addition, knowledge of risk factors for PPH can be used to ensure that women at high-risk deliver in an appropriate facility, but haemorrhage cannot be entirely prevented by identifying risks.

Overall it has been concluded that only 10-30% of women deemed to be at high risk in pregnancy develop any pregnancy complication.(Carroli et al., 2001) Therefore, in resource poor settings, directing efforts solely at those deemed to be at 'high risk' may inappropriately disadvantage others. For pre-eclampsia, there is clear benefit of risk prediction (an opportunity to offer evidence-based prophylaxis) and an early phase in the disease progression where increased monitoring is beneficial. In sepsis and haemorrhage this is less clear as in all cases immediate treatment is vital. Therefore, health services must be able to regularly monitor and act quickly in response to abnormalities once they occur.

1.4.2 Vital signs measurement for early detection of pregnancy complications

Failure to accurately measure, understand and act on abnormal BP in pregnancy results in increased mortality and morbidity.(Cantwell et al., 2011, McCaw-Binns et al., 2004) Measurement of BP is clearly essential for diagnosis of HDP, but evidence that BP alone

predicts pre-eclampsia and resulting morbidity and mortality is more challenging. One large systematic review (n=60,599 women; n=3341 pre-eclamptic women) found that mean arterial pressure was better at predicting pre-eclampsia than systolic BP (sBP) or diastolic BP (dBP) (AUC 0.76; 95% CI 0.70-0.82 compared to 0.68; 0.64-0.72 and 0.66; 0.59-0.72 respectively).(Cnossen et al., 2008) This study was limited by heterogeneity in the studies in terms of baseline risk, but it was concluded that BP measurements at the first antenatal visit in the first or second trimester for healthy, normotensive women does not help predict pre-eclampsia. It has also been concluded that pre-diagnosis measurement of BP is only a moderate predictor of adverse maternal outcome (AUC 0.68; 95% 0.29-0.92.(Thangaratinam et al., 2011a) In practice, this is a low-cost test that is highly acceptable. Consequences of missing a diagnosis of early onset pre-eclampsia, or failing to diagnose chronic hypertension are severe, and therefore measurement of BP in early pregnancy remains normal practice.

The thresholds of hypertension used to diagnose pre-eclampsia internationally are recognised as ≧140/90 mmHg with severe hypertension defined as ≧160/110 mmHg.(National Institute for Health and Care Excellence, 2010, Tranquilli et al., 2014, Magee et al., 2008, The American College of Obsteticians and Gynaecologists, 2013, Brown et al., 2018) However, the evidence that supports these thresholds is primarily limited to cohort or case control studies rated as moderate quality evidence.(Magee et al., 2008, The American College of Obsteticians and Gynaecologists, 2013) Once pre-eclampsia is diagnosed, evidence from several prospective, multicentre cohort studies suggests that elevated BP is associated with increased risk of maternal adverse outcome. For example, a cohort of 1547 women with pre-eclampsia in South Africa demonstrated that increasing systolic BP (above 140 mmHg) was associated with an increased risk of kidney injury, magnesium sulfate use and critical care unit admission, but that the rate of eclampsia and maternal death was similarly high across the range of systolic BP, as shown in Figure 6 on page 52.(Nathan et al., 2017) Two further

prospective studies have demonstrated that elevated BP is associated with a composite of adverse outcomes including eclampsia, maternal death, hepatic and renal dysfunction, both in a high (n=2023) (von Dadelszen et al., 2011) and low-income settings (n=2081),(Payne et al., 2014) although the number of women in which these events occurred was low and thresholds of hypertension were not explored.

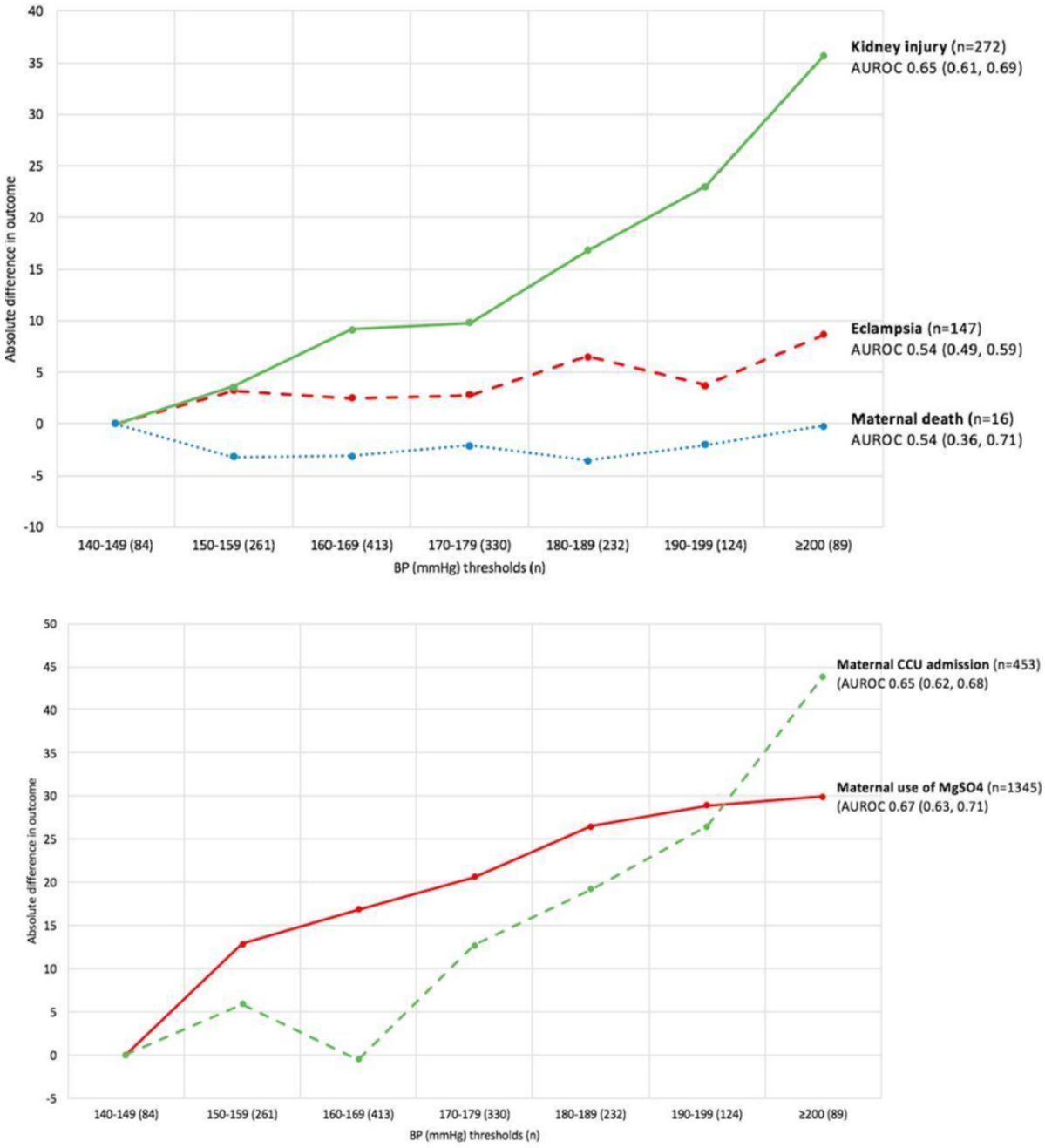


Figure 6 Maternal and process outcomes as systolic blood pressures increase (Nathan et al., 2017)

High quality population level data over seven years has demonstrated that pregnancy-associated stroke is 5.2 times more likely to occur in women with HDP and that resulting complications were also more common (n=9,890).(Leffert et al., 2015) The rarity of the disease means that even rigorous case-control and cohort studies have few cases. However, it has been demonstrated that the higher the BP, the greater the risk of stroke (n=30; OR 1.08; 95% CI 1.3-1.13) (Scott et al., 2012) and that risk is greater in severe pre-eclampsia compared to all pre-eclampsia.(Cleary et al., 2018) Whilst causality cannot be determined from observational data, the prevalence of stroke decreases as the proportion of patients receiving antihypertensives increases.(Cleary et al., 2018) Evidence is conflicting as to whether systolic BP or diastolic BP are more strongly associated with the risk of stroke,(Martin et al., 2005, Scott et al., 2012) but all are in agreement that higher BP increases the risk.

All of these studies are confounded by treatment paradox, as shown in the paper by Nathan et al.. Therefore, in LIC, where BP treatment may be suboptimal, risks of morbidity from elevated BP may be even greater. Overall, BP measurement is clearly essential for diagnosis of pre-eclampsia and higher BPs after diagnosis are associated with adverse outcomes. Therefore, regular monitoring is required for early detection and prevention of pre-eclampsia as well as treatment after diagnosis in order to prevent maternal morbidity and mortality.

Vital signs measurement is also key in the early detection of shock caused by sepsis or haemorrhage. The definition of sepsis has recently changed, but all current guidelines include detection of abnormal vital signs.(The UK Sepsis Trust, 2017, Royal College of Obstetricians and Gynaecologists, 2012) These are adapted from the original definition of the systemic inflammatory response syndrome (SIRS) created for non–pregnant adults and based on expert consensus.(Bone et al., 1992) In normal pregnancy, white cell count is increased, HR increases by 10-15 bpm by term, and in labour, HR and

respiratory rate increase substantially.(Broughon Pipkin, 2007) A recent systematic review identified from 87 studies (n=8834) that healthy maternal physiological parameters in the second and third trimester overlap with all the SIRS criteria except temperature.(Bauer et al., 2014) Therefore, the current criteria are not adequate to diagnose sepsis in pregnancy. The SIRS criteria have therefore been modified for use as shown in Table 2 below. These changes are based on expert opinion and knowledge of pregnancy physiology as opposed to specific evidence.(Royal College of Obstetricians and Gynaecologists, 2012) Data demonstrating the association between adverse vital signs in sepsis and maternal morbidity and mortality is scarce. Only small case series and observational studies have shown that BP and stroke volume were lower in patients with septic shock who died compared to those that survived.(Mabie et al., 1997)

Table 2 Criteria for diagnosis of sepsis in pregnancy and outside of pregnancy

	SIRS/Sepsis Criteria (non-pregnant) (Bone et al., 1992)	**RCOG Bacterial Sepsis Guideline (Royal College of Obstetricians and Gynaecologists, 2012)**	**UK Sepsis Trust Inpatient Maternal Sepsis Tool (The UK Sepsis Trust, 2017)**	
			Amber Flag Criteria	**Red Flag Criteria**
Temperature	>38°C or <36°C	>38°C or <36°C	<36°C	-
Heart Rate (beats per minute)	>90	>100	100-130	>130
Respiratory Rate (breaths per minute)	>20 or PaCO2 <32 mmHg	>20	21-24 or breathing hard	>25 or needs oxygen to keep SpO2> 92%
Inflammatory Variables	>12 x 10^9 per litre	>12 x 10^9 per litre or leucopenia or normal WBC with >10% immature forms or CRP >7mg/l	-	-
Blood Pressure (mmHg)	*Septic Shock:* Systolic <90 or reduction of =40 from baseline	Systolic <90 or reduction of =40 from baseline or mean arterial pressure <70	Systolic 91-100	Systolic BP <90
Other	-	Impaired mental state, significant oedema or positive fluid balance, hyperglycaemia in absence of diabetes, lactate ≥4, mottling,	Deterioration in functional ability, prolonged rupture of membranes, recent invasive procedure, bleeding/wound infection/vaginal discharge non-reassuring CTG	Unresponsive, non-blanching rash, mottled/ cyanotic, not passed urine in 18 hours or urine output <0.5 ml/kg/hr, lactate ≥2.

Alongside the measurement of HR and BP, Shock Index (SI), is a promising marker of compromise in pregnancy. SI is the ratio of HR to sBP. In the non-pregnant population, it was proposed as an earlier marker of blood loss in patients with gastrointestinal haemorrhage over 50 years ago.(Allgower and Burri, 1967) The potential for SI as a predictive marker in pregnancy was first explored in women with early pregnancy complications.(Birkhahn et al., 2002, Birkhahn et al., 2003) More recently, a number of case-control studies have explored the use of SI in obstetric haemorrhage.(Le Bas et al., 2014, Sohn et al., 2013, Kohn et al., 2018) These small, retrospective studies demonstrated that SI is significantly higher in those with PPH,(Kohn et al., 2018) those receiving a blood transfusion,(Borovac-Pinheiro et al., 2018, Sohn et al., 2013, Kohn et al., 2018) and those requiring hysterectomy, compared to controls with a normal blood loss at delivery.

It is also suggested from a small, retrospective, case-control study that SI and delta SI (difference between peak and baseline SI) are strong predictors of PPH, transfusion and need for surgical intervention compared to HR and systolic BP.(Kohn et al., 2018) These findings are supported by two further large prospective cohorts of women with PPH which found that SI was a more consistent predictor of adverse maternal outcome (Intensive Care Unit (ICU) admission, blood transfusion, invasive surgery (Nathan et al., 2015c) (El Ayadi et al., 2016) and maternal death (El Ayadi et al., 2016)) compared to individual components of HR, BP or mean arterial pressure. In both studies, significance was only demonstrated for some comparisons and the severity of PPH differed (El Ayadi et al. included PPH >750ml in Egypt and Nigeria and >500ml in Zambia and Zimbabwe; Nathan et al. included PPH >1500ml). However, these reports suggest that SI may be a useful measure of early compromise following delivery.

Despite the growing evidence that SI may be useful in haemorrhagic shock, a systematic review identified only five studies that have examined the use of SI in predicting clinical

outcomes in septic shock (Tseng and Nugent, 2015). None of these were undertaken in a pregnant population. These small, retrospective studies used different thresholds and different outcomes, yet all concluded that elevated SI was associated with increased morbidity,(ICU transfer,(Rady et al., 1992) organ failure (Kenzaka et al., 2012, Wira et al., 2014)) and mortality.(Berger et al., 2013, Yussof et al., 2012) The physiological changes in pregnancy mean that the thresholds derived in the earlier studies are unlikely to be directly comparable to a pregnant population. Given the promising data in the general population, and known risks of sepsis in pregnancy, further research in the maternity population is required.

Overall there is clear evidence that elevated BP is associated with maternal morbidity and mortality. Evidence demonstrating the association between adverse vital signs and sepsis and haemorrhage is less clear, but promising novel markers such as SI exist. All the leading causes of maternal death are directly related to abnormal vital signs meaning that measurement is vital for the detection and early treatment of the pregnancy complications.

1.4.3 Equipment for early detection of pregnancy complications

Despite the clear indication for vital signs measurement there are challenges in accurate technique and equipment. Auscultation using a mercury sphygmomanometer is a relatively low-cost technique but requires a skilled observer to accurately auscultate the Korotkoff sounds to the nearest 2mmHg. Previous studies of 28,841 pregnant women have demonstrated that accurate BP recording infrequently occurs; 78% of BP readings were documented as ending in a zero and 15% to even digits other than zero.(Wen et al., 1993) This is known as terminal digit preference and potentially leads to misdiagnosis and therefore under-treatment of hypertension. In non-pregnant adults, those visiting general practices with higher levels of terminal digit preference had significantly lower odds of having an antihypertensive prescription (OR 0.92; 95% CI 0.85-0.99).(Nietert et

al., 2006) In pregnancy, this could be exposing the woman and baby to increased risk by failing to recognise and treat hypertension.

Mercury columns in sphygmomanometers are now not in use in Europe due to concern over toxicity. Aneroid devices have replaced mercury columns but still rely on accurate auscultation and are therefore subject to the same observer error. They also require more regular maintenance and calibration than mercury devices, with studies demonstrating that 53% of aneroid devices in the UK General Practice read an error of more than +/- 3mmHg, which is significantly more than mercury or automated devices (8%).(Coleman et al., 2005)

Automated BP devices use oscillometry to avoid the necessity of auscultation by a skilled user. It is recommended by the British Society of Hypertension (O'Brien et al., 1993) and the European Society of Hypertension (O'Brien et al., 2010) that automated devices are independently validated to ensure accuracy. This involves comparing them to mercury devices against a strict standardised protocol. In pregnancy, there are substantial haemodynamic changes including increased BP, stroke volume and decreased peripheral vascular resistance.(Broughon Pipkin, 2007) Therefore, it is important that devices are validated as accurate specifically in pregnancy. A recent systematic review identified that out of the hundreds of commercially available devices, just 28 have been examined in pregnancy and only nine devices passed validation in pregnancy without violating the validation protocol (e.g. inclusion of too few pregnant women).(Bello et al., 2018) Additionally, automated devices are also prone to underestimate BP in women with pre-eclampsia and therefore a separate validation is required for this group. The systematic review identified just four automated devices accurate in pre-eclampsia.(Bello et al., 2018) These devices usually require power to automatically inflate the cuff and therefore need the purchase of batteries (which are costly) or electricity, both of which can be intermittent in LIC.

In addition to the accuracy of equipment, it is also vital that equipment is readily available. In 2012 the WHO listed BP equipment as a key commodity to identify and treat hypertension.(The Partnership for Maternal Newborn & Child Health, 2011) Despite this, it is frequently reported that access to reliable equipment is poor. Data reporting the availability of BP equipment in maternity care in LIC is mainly drawn from small cross-sectional studies which report availability of between 62% (Abdu et al., 2017) and 88% of facilities.(Ziraba et al., 2009, Penfold et al., 2013) Some national reports are available; for example, in Tanzania in 2014-15 health facility surveys identified that 49-100% (mean 72%) of facilities providing antenatal care had equipment to measure BP,(Ministry of Health and Social Welfare Tanzania, 2014-2015) although this does not indicate whether the supply was sufficient to meet the patient demand, the accuracy of devices available, or whether they were functioning. Most recently, a cluster RCT in Mozambique demonstrated that increasing availability of equipment, as part of a multi-faceted package of antenatal care, resulted in increased number of women having BP screening at antenatal visits.(Betrán et al., 2018) Therefore, despite the clear necessity to measure BP, access to appropriate equipment remains a problem globally.

It is also vital there are sufficient numbers of adequately trained staff to use equipment (explored in Section 1.4.4 below). Whilst the role of BP self-monitoring is being explored in trials in HIC, widespread dissemination of devices is unlikely to be feasible in LMICs, particularly in settings where many facilities even lack BP devices. Novel technologies aiming to improve skill or promote task sharing are explored in Section 1.4.5. Finally, women must present early and regularly enough to receive benefit. Strengthening service delivery, including provision of equipment, is an important strategy to improve demand by improving perception of quality of care and access to high quality care.(United Nations Commissioners Report, 2012)

1.4.4 Skills for early detection of pregnancy complications

Recognition of maternal risk and early haemodynamic compromise requires trained HCP. Figure 7 on page 60 shows the 57 countries worldwide that have a critical shortage of HCP, meaning their workforce is beneath the threshold of 2.5 HCP (doctors, nurses and midwives) per 1000 population required for >80% coverage of essential obstetric interventions.(World Health Organisation, 2006) The majority of these are in sub-Saharan Africa and rural areas are disproportionately affected. High quality evidence, using comprehensive estimates of health personnel from 117 countries and robust regression for confounders, concluded that the availability of HCP was significantly associated with maternal and infant mortality.(Anand and Bärnighausen, 2004) Whilst causality cannot be shown, this is supported by evidence from five African countries where shortages of HCP reduces the number of facilities that can offer basic and comprehensive obstetric care.(UNFPA, 2003) A narrative review identified little published research defining the exact effects of staff shortages on the quality of maternal health care, but potential mechanisms explored were increased workload, increased waiting times, reduced time to care for patients, poor infection control and reduced job satisfaction and morale.(Gerein et al., 2006)

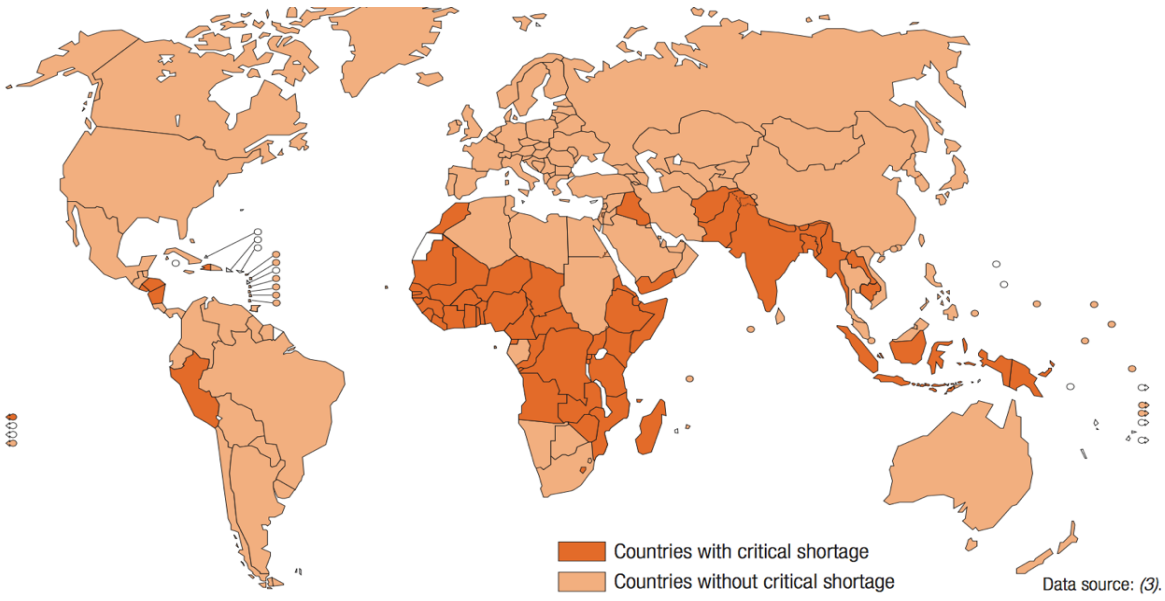


Figure 7 Countries with a critical shortage of health service providers (World Health Organisation, 2006)

Meeting the shortfall would require the number of HCP to increase by three-fold by 2030, requiring significant investment beyond the capacity of most LMIC.(World Health Organisation, 2006) Therefore, the WHO advocated increasing community participation and intentionally substituting tasks to HCP of a lower cadre, or creating new professional or non-professional cadres.(World Health Organisation, 2005b) This is known as task-sharing or task-shifting. The aim is to increase the efficiency and provision of health care and reduce the time taken to increase the workforce. Task-sharing can take many different forms but multiple systematic reviews have concluded that it is an important policy option since clinical outcomes in maternity care (Fulton et al., 2011, Dawson et al., 2014) and related fields such as HIV care,(Callaghan et al., 2010) primary care (Laurant et al., 2005) and neonatal and under 5 morbidity (Lewin et al., 2010) are comparable when provided by lower or new cadres of HCP compared to traditional HCP. However, it is recognised that adequate training and guidance is required.(Fulton et al., 2011)

The majority of evidence for task-sharing in maternal health in LMIC applies to training community health workers (CHW). In 2010, a systematic review identified 44 studies, almost all of which showed a significant impact on reducing maternal, perinatal and neonatal mortality and improving service utilisation.(Global Health Workforce Alliance, 2010) Four of these studies were specific to early detection of pregnancy complications in LMIC and all but one demonstrated a significant improvement in detection of pregnancy complications and referrals by CHW with some benefit in clinical outcomes.(Global Health Workforce Alliance, 2010) However, the robustness of the methodology in these four studies was mixed.

More recently one randomised study and several quasi-experimental and observational before-and-after studies report that training CHW to provide community education and home visits can improve women's awareness of danger signs in pregnancy.(Jennings et

al., 2011, Darmstadt et al., 2010) This also improved process outcomes such as the number of women receiving antenatal care and skilled birth attendant services,(Jacobs et al., 2018, Deller et al., 2015, Midhet and Becker, 2010, Adam et al., 2005) which has the potential to improve early detection of pregnancy complications. There is increasing interest in training CHW to detect, monitor and initiate treatment of specific conditions in the community, as opposed to providing health promotion or referring based on symptoms alone. For example, a multicentre cluster RCT is evaluating whether training CHWs to monitor BP and initiate treatment based on an electronic algorithm can reduce morbidity and mortality from HDP has recently been completed.(Khowaja et al., 2016) However, as yet, evidence that CHW activity in early detection of pregnancy complications directly reduces morbidity and mortality is elusive. As it is known that delays in deciding to attend and physically reaching care can be critical, CHWs have the potential to improve this and therefore, further research is warranted.

The studies above explore formalised task-sharing where specific roles and duties are identified and planned. However, the principle of delegating tasks, and informal or opportunistic task-sharing is an ongoing coping mechanism in understaffed facilities. Therefore, this is common in LIC, although it is harder to quantify its existence and impact.(Dovlo, 2004) For example, qualitative evidence frequently reports that CHWs routinely measure BP and assess basic vital signs within health care facilities.(Akeju et al., 2016) Formal task-sharing requires adequate political and financial commitment to ensure that it is integrated within the health system and sustainable.(Fulton et al., 2011) In practice, research that involves training of HCP in LMIC may also consider the contribution of informal task providers in each context, who may provide a significant proportion of routine services and also be impacted by any health intervention.

Another key strategy in maximising the efficiency and capacity of the workforce is to ensure that all HCP have the correct knowledge and skills. When considering early

detection, there is moderate evidence from multiple countries, using knowledge tests, skills tests and direct observation, that HCP may not have the desired level of knowledge and skill regarding pregnancy complications. (Harvey et al., 2004, Boene et al., 2016, Sheikh et al., 2016, Stellenberg and Ngwekazi, 2016) In a multi-country study in Benin, Ecuador, Jamaica and Rwanda, the proportion of HCP answering correctly on the diagnosis and management of PPH (63%), HDP (63%) and sepsis (44%) was low.(Harvey et al., 2004) This correlated with inadequate monitoring of vital signs during labour and postpartum.(McCaw-Binns, 2004, Gbangbade, 2003)

A systematic overview of reviews of educational interventions in maternal health in LMIC (n=18) and HIC (n=6) included 23 studies. The components of the educational interventions varied but they are likely to have included the three main causes of maternal mortality. They found that the most effective educational interventions at changing professional practice were multifaceted, including two or more factors such as educational materials, outreach visits, local opinion leaders and audit and feedback (10 reviews with a range of positive results). Some single interventions such as audit and feedback and off-site educational meetings showed some positive effect on professional practice but others such as passive distribution of educational materials did not, and none correlated with clinical outcomes.(Althabe et al., 2008) Very few studies explored the effect on clinical outcomes. More recently a systematic review identified several high-quality trials which demonstrated changes in behaviour and improvement in rates of PPH, eclampsia and maternal death following multifaceted Emergency Obstetric and Neonatal Care training, of which detecting and managing pregnancy complications is a key component.(Bergh et al., 2015)

A recent Cochrane systematic review of 26 studies (24 cluster RCTs, 2 quasi-randomised/controlled trials) identified that community intervention packages (in addition to routine CHW tasks) reduced maternal morbidity (RR 0.75; 95% CI 0.62-0.92), with a

reduction in the incidence of haemorrhage but not eclampsia or puerperal sepsis. Strength of evidence for a reduction in maternal mortality was borderline (RR 0.80; 0.64-1.00).(Lassi and Bhutta, 2015) However, the packages contained multiple components. When considering CHW education and home visits alone, the effect was not seen, although this may be due to inadequate sample size as only two of the studies were included in this analysis.(Lassi and Bhutta, 2015)

Early detection of pregnancy complications is dependent not just on reliable equipment but also on the capacity of HCP. Interventions aiming to improve the efficiency and availability of staff by task-sharing show promise, as do educational interventions. Therefore, studies aiming to improve maternal mortality and morbidity by early detection should carefully consider which HCP should be involved and ensure that training components build upon the existing literatures by including appropriate methods.

1.4.5 Early Warning Scores

Whilst measurement of vital signs is clearly critical for detection and monitoring of pregnancy complications, identification of abnormal results and action is required in order to prevent morbidity. In recognition of this, the 2003-2005 Confidential Enquiry into Maternal and Child Health report recommended the use of an early warning system (EWS) such as the modified early obstetric warning system (MEOWS).(Lewis, 2007) This is a tool to allow for tracking of vital signs according to thresholds of physiological parameters. When abnormal vital signs are identified and plotted, normally the colour of the paper (yellow or red) highlights the severity of deviation from normal, and therefore the need to escalate care.

A recent national survey demonstrated that these are widely used across maternity units in the UK (100% of 130 respondents).(Isaacs et al., 2014) However, there is considerable variation in the design, the process to escalate care and the thresholds that trigger action,

where only 13% of 120 maternity units used the combination of 'normal' ranges described in the Confidential Enquiry into Maternal and Child Health report (HR, 50–99 bpm; RR, 11–20 breaths/min; sBP, 100–149 mmHg; dBP, ≤89 mmHg; SpO2, 95–100%; T, 36.0–37.9°C; and conscious and alert).(Smith et al., 2017) This is likely because of the lack of evidence supporting individual or combinations of thresholds for predicting morbidity in pregnancy as previously described. Current thresholds are either not referenced or cite physiological changes in pregnancy described in a reference book based on individual small studies.(Chamberlain, 1998) Two ongoing studies aim to address this.(Loerup et al., 2016, Kumar et al., 2017)

There are six systematic reviews of EWS studies looking at development, predictive performance and impact, but all exclude the maternity population.(Gerry et al., 2017) In total, eight studies have examined the predictive capacity of EWS for maternal morbidity and mortality. A small prospective, single centre study demonstrated a good sensitivity (89%) and specificity (79%) for identifying morbidity such as haemorrhage, hypertensive disease and infection.(Singh et al., 2012) This was higher than the efficacy of EWS found in non-pregnant adults,(Gao et al., 2007) which is likely due to the lower threshold of morbidity included, where triggering an EWS with hypertension perhaps unsurprisingly is associated with a diagnosis of pre-eclampsia. However, evidence for its use in severe morbidity is provided by two, small retrospective case-control studies where elevated EWS was associated with ICU admission.(Ryan et al., 2017, Hedriana et al., 2016) In addition, Carle et al. demonstrated retrospectively that in 2200 obstetric admissions to ICU in the UK, three different variations of MEOWS chart, statistical review of cases and existing EWS, all had high predictive capacity for maternal mortality (Figure 8, n=32) (Carle et al., 2013). Paternina-Caicedo et al. found similar results in retrospective study of a low-resource population (n=702; 29 maternal deaths) despite using slightly different thresholds.(Paternina-Caicedo et al., 2017)

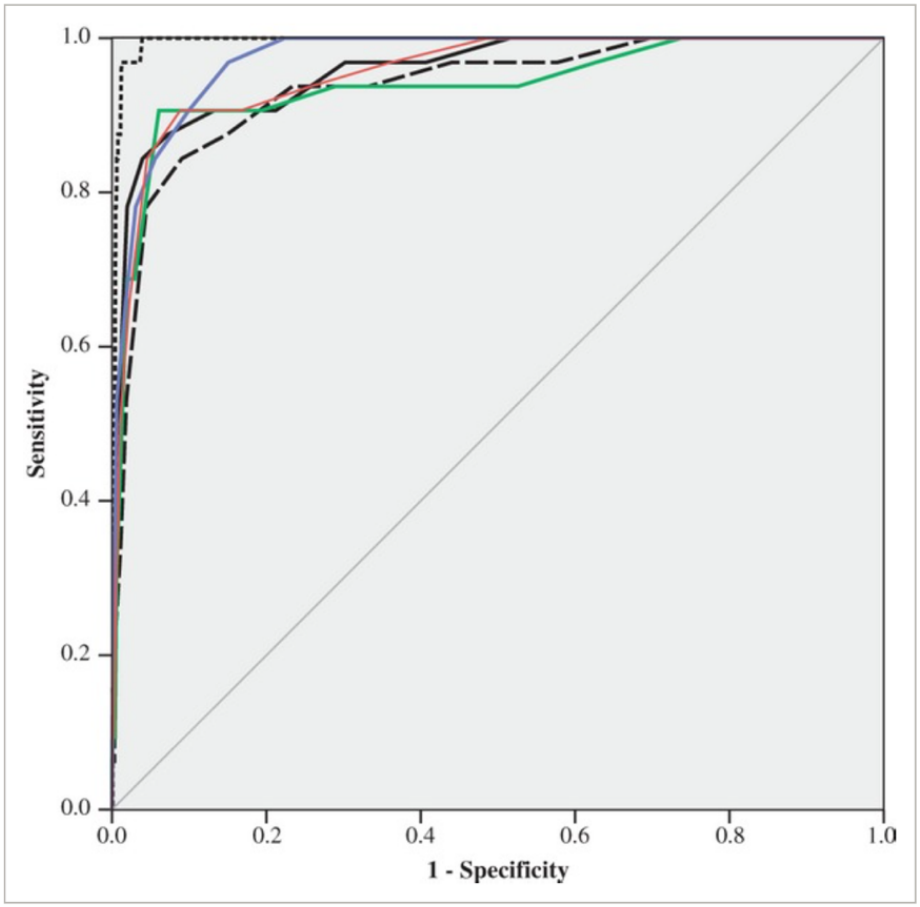


Figure 8 Receiver operating characteristic curves comparing obstetric early warning scores for maternal mortality. Dotted: modelled EWS; Solid: clinical EWS; dashed: clinical EWS excluding RR (due to missing data); blue: National Early Warning Score (non-obstetric); red: Modified Early Obstetric Warning System green: Confidential Enquiry into Maternal and Child Health; grey line: reference (Carle et al., 2013)

Two studies looked retrospectively at the capacity of seven different EWS to predict sepsis in 913 women with chorioamnionitis. Both concluded that EWS had a low specificity for sepsis and thus were poor predictors.(Lappen et al., 2010, Edwards et al., 2015). However, the lack of confirmed microbiological diagnosis of chorioamnionitis, large amount of missing data (>50%) and small number of women with an outcome (n=5) limits the use of this finding. Additional tools are under development but currently there is no evidence to recommend their use.(Bartlett et al., 2016) There are a number of additional scores aiming to predict risk of morbidity and mortality from sepsis but only one has been developed specifically for an obstetric population, the Sepsis in Obstetrics Score. A small, retrospective cohort study found this to be a good predictor of ICU

admission in women presenting to the emergency department with suspected sepsis (n=850) (AUC 0.92, sensitivity 88.9%, specificity 95.2%).(Albright et al., 2014) But, in a population with confirmed sepsis admitted to ICU it was no better at predicting mortality than tools established for the non-obstetric population. Perhaps unsurprisingly, the best functioning tool in this high-risk ICU population was one that measured multiple organ dysfunction.(Aarvold et al., 2017) Whilst this study included data from Pakistan and Brazil, the requirement to test creatinine, bilirubin, platelets and arterial oxygen limits its application in most LIC settings.

All these studies have few cases of morbidity and mortality due to its rarity in the maternity population. Those undertaken in highly selective populations in high-income ICU settings are unlikely to be representative of the general obstetric population, in high or low-income settings. Despite this, the lack of evidence-based thresholds and the numerous scores available, there is initial evidence that EWS may be beneficial in predicting morbidity and mortality in pregnancy. These systems may be of greatest benefit where delays in treatment are known to contribute to maternal mortality, therefore further investigation in LIC is warranted.

Despite this promising advance, there is no robust evidence demonstrating that use of EWS clinical prevents morbidity and mortality. An unblinded, retrospective case review of 112 women admitted to maternal ICU or HDU concluded that five could have been avoided if EWS had been used.(Austin et al., 2014) One non-randomised pilot study implemented an EWS across six hospitals and demonstrated a significant reduction in maternal morbidity compared to 23 other hospitals,(Shields et al., 2016) without describing the components of the outcome, the differences in hospitals or relevant adjustments. Two small before-and-after studies have been undertaken, one concluding that EWS improved vital signs measurements in women with bacteraemia (n=17),(Maguire et al., 2015) whilst the other reported improved pre-operative

stabilisation (n=85) and action in response to abnormal results (n=45).(Merriel et al., 2016) Neither had sufficient numbers to demonstrate any benefit in clinical outcomes. Despite the lack of evidence, they are still consistently recommended due to the intuitive appeal that delays in responding to abnormal vital signs contributes to mortality.(Lewis, 2007) Therefore, further research to examine the clinical effectiveness of EWS in high and low-income settings is required.

In order for EWS to be useful, they require accurate measurement and documentation of vital signs followed by appropriate escalation of care. The significance of this interaction with HCP is rarely acknowledged in the described papers, despite substantial missing data. Studies in the general population have demonstrated that these processes are subject to error such as inadequate frequency of monitoring,(National Confidential Enquiry into Patient Outcome and Death, 2005) incomplete data,(Chen et al., 2009) inaccurate calculation of EWS (Edwards et al., 2010, Mohammed et al., 2009) and poor legibility of documentation.(National Confidential Enquiry into Patient Outcome and Death, 2005) Randomised, prospective data in the general population also concluded that only 38% of patients with an abnormal result were correctly escalated.(Niegsch et al., 2013) Whilst uptake of EWS across UK maternity units is almost unanimous, a national survey identified many barriers to its use including lack of training (22%); insufficient staff (20%) or time to complete it (10%) and lack of priority compared to other competing clinical duties (12%).(Bick et al., 2014)

The importance of EWS as a behavioural intervention, working within the social, organisational health system, was highlighted by a systematic review and qualitative synthesis of EWS in the general population.(Connolly et al., 2017) From 10 studies, undertaken in HIC, they identified several important themes including that staff felt that EWS was useful in supporting and building confidence in clinical judgement and supported communication when escalating care.(Connolly et al., 2017) However, regular

false alarms were noted to result in ‘alarm fatigue’ if thresholds did not appear to be appropriate for individual patients and the additional burden of documentation was perceived to increase workload.(Connolly et al., 2017) Only one study in a HIC has rigorously explored the behavioural effect of EWS in maternity staff. EWS were similarly found to enable communication and shared understanding of pregnancy complications between HCPs, but the additional burden of work meant that HCP exercised professional discretion in choosing when to use it, which reduced the potential effectiveness.(Mackintosh et al., 2014) Staffing pressures are perceived as the greatest barriers to their use,(Isaacs et al., 2014) and this is likely to be of even greater significance in overwhelmed, low-resource environments where the challenges of contextual and political environment are likely to be different. Therefore, further research on the efficacy and mechanism of action of EWS is required prior to introduction internationally.

Technologies that incorporate EWS calculations and alert HCPs to abnormalities may present a novel solution by reducing errors in paper-based recording, workload and delays in communication. For example, VitalPAC is a software system that prompts HCP to complete vital signs at appropriate intervals and automatically analyses and raises alerts in response to changes in vital signs. Before-and-after studies have demonstrated that its use improves accuracy of documentation in a high-acuity emergency department (Pullinger et al., 2017, Schmidt et al., 2015) in addition to non-maternity clinical outcomes (Mitchell et al., 2016) including in mortality.(Schmidt et al., 2015) However, the observational, uncontrolled design of these studies limits interpretation of findings. Additionally, it may require transcription of vital signs into the system which may be associated with error and present an additional burden of work. It also requires technologies that are not widely available in LIC.

The Microlife CRADLE Vital Sign Alert (VSA) device is a semi-automated hand-held upper arm device that measures HR, BP and automatically calculates SI. It has been validated as accurate outside of pregnancy (de Greeff et al., 2008) as well as in pregnancy, including women with hypertension (Nathan et al., 2015b) or hypotension.(Nathan et al., 2015a) The method of testing HR involves calculating the average interval between heart beats and then discarding intervals that are more or less than 25% of the average and using the remaining intervals to calculate the pulse rate.(Lin, 2016) It has been developed specifically for use in LIC, with low power requirements and a built-in, rechargeable battery that can be charged with a micro-USB (the same as most international phone chargers). Results are shown on a digital display as well as an EWS traffic light. The lights are triggered by both hypertension and SI as shown in Figure 9 on page 71 alerting all users to abnormal results and the need for action. Qualitative data (155 interviews with HCPs and 41 with pregnant women and their families) have indicated that HCPs found the CRADLE VSA easy to use and that the traffic light EWS improved confidence in decision-making and professionalism (Nathan et al., 2018a) but the study did not explore the impact of the traffic light EWS on clinical management and its impact on morbidity and mortality is unknown.

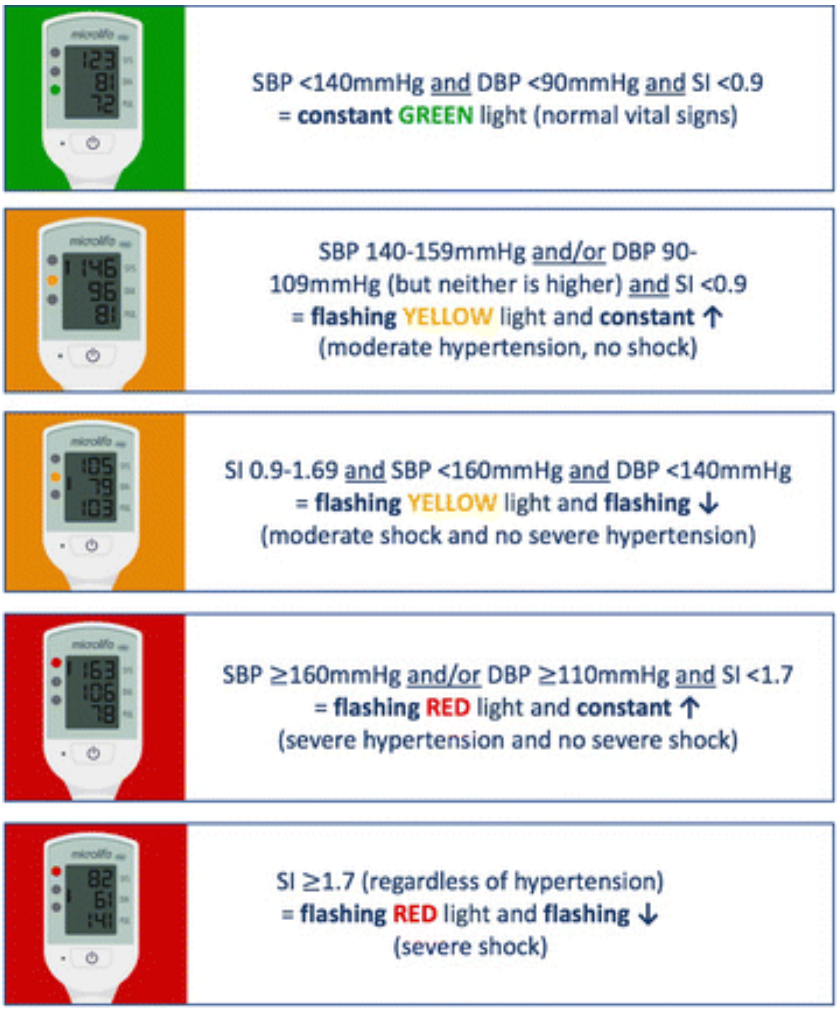


Figure 9 Thresholds for traffic light EWS alerts on the CRADLE VSA

In summary, vital signs measurements are key in the diagnosis and monitoring of pregnancy complications but there are challenges in technique, availability of accurate equipment and trained staff which mean that care is sub-optimal. Promising innovations exist to overcome these challenges, but none have been tested in low-resource settings.

1.4.6 Strategies to prevent morbidity following early detection of pregnancy complications

The availability of trained HCP and equipment has been explored in the previous sections. Whilst not the direct focus of Section 1.4, sufficient resource to transfer or treat the identified pregnancy complication is required in order to prevent mortality. The 2016

United Nations review of essential commodities for maternal and child health identified that 19% of health facilities across 12 LMIC had supply issues with oxytocin, 73% with misoprostol and 46% with magnesium sulfate.(Pronyk et al., 2016) However, simply counting the availability of commodities is only a crude measure of capacity to treat pregnancy complications, since supplies also need to be reliable, functional and with sufficient population coverage, together with appropriately trained personnel to use them. In order to reach a facility with appropriate care, referral may be required. A systematic review of integrated packages of care to reduce maternal mortality concluded that all programmes which successfully reduced maternal mortality had functioning referral systems and appropriate supply of drugs and equipment.(Nyamtema et al., 2011) Referral can mean self-referral or inter-referral to higher level facilities. The key components of an effective referral have been identified as:(Murray et al., 2001)

- An adequately resourced referral facility
- A system of communications and feedback
- Designated transport
- Protocols for identifying complications
- Personnel trained to use the protocols
- Teamwork across referral levels
- A system of documentation

In LMIC there are multiple factors that impede these processes such as geographical terrain, lack of transport, distribution of health facilities or lack of formal communication systems. In addition to external factors, failure to consider these components may result in poor quality referrals, which in itself presents a problem. A systematic review of referral practice in India demonstrated from three qualitative and 16 quantitative studies that between 25-52% of pregnant women are referred after being identified as high-risk antenatally and 25-36% of low-risk cases are referred after experiencing a pregnancy complication.(Singh et al., 2016) This high level of referral represents a significant impact on services, which is potentially misaligned when the proportion of high-risk pregnant

women that go on to develop a complication is low, as previously described. The studies identified absence of referral records, inadequate stabilisation prior to referral and low levels of compliance as common problems. They concluded that poor referrals can contribute to the second and third delay (discussed in 1.3.4) as shown in Figure 10 on page 73. Qualitative studies identified low skills and confidence in staff, confusion over criteria for referral and lack of communication and supervision.(Singh et al., 2016)

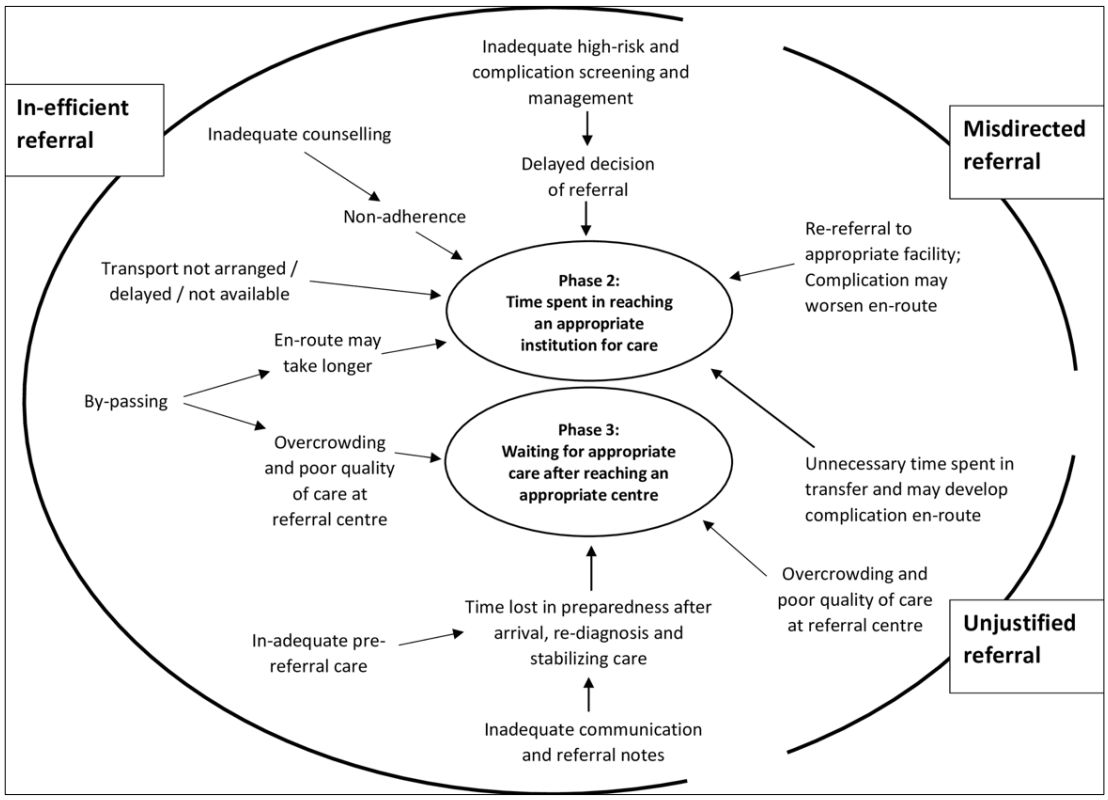


Figure 10 Inappropriate institution-referrals and contribution to delays in access to emergency obstetric care (Singh et al., 2016)

The proportion of referrals into facilities reported in India are higher than those reported in other smaller studies from sub-Saharan African countries where between 27% (Pembe et al., 2010) and 29% (Majoko et al., 2005) of antenatal patients are referred. This may be due to different skill levels of HCP at peripheral facilities. However, the reported challenges were similar with low levels of compliance and inadequate guidance or adherence to guidance.(Pembe et al., 2010, Majoko et al., 2005) There is limited evidence to suggest that interventions aiming to overcome Phase 2 delays in obstetric

emergencies correlate with improved clinical outcomes.(Hussein et al., 2012) However, the majority of studies included in the review were aimed at self-referrals not referrals between institutions which is more likely to reflect cases in need.

In conclusion, there are effective interventions to treat the leading causes of maternal mortality and morbidity worldwide; however, current models do not adequately identify who is at greatest risk. Therefore, all women require regular monitoring of vital signs to ensure that pregnancy complications are diagnosed in time for treatments to be effective. This is complicated by inadequate access to reliable equipment and insufficient trained staff. Interventions that aim to improve early detection by increasing the number of staff and understanding of staff about early detection show promise, but this must occur in combination with adequate access to equipment in a functional referral system for lives to be saved. Future research should explore the efficacy of novel solutions in LMIC where the burden of disease is greatest and access to effective interventions will save lives.

1.5 Trial designs to evaluate complex interventions aiming to improve maternal morbidity and mortality in low resource settings

The evidence for interventions in early detection of pregnancy complications has been explored in Section 1.4 and the quality of this evidence is often poor. Failure to accurately demonstrate efficacy (or not) of an intervention means that potentially effective interventions cannot be readily incorporated into policy. This section describes the key methodological considerations when evaluating an intervention aiming to reduce maternal mortality and morbidity in LMIC.

1.5.1 Cluster Randomised Controlled Trials

RCTs are the 'gold standard' for determining the efficacy of an intervention. They can be classified by the extent of blinding, number of treatment arms or the method of randomisation.(Vader, 1998) RCTs can be randomised at the level of the individual or a cluster, the latter meaning that a group is randomised, for example, the geographical area or health care facility. Cluster RCTs are increasingly used in health services and policy research, where the intervention is delivered across a group, and individual randomisation would not be appropriate.(Eldridge S, 2012)

Cluster RCTs can also be classified by the timing of exposure to the intervention. In standard parallel cluster RCTs, half the clusters are randomised to the intervention and half to the control at the beginning of the trial. As parallel cluster RCTs usually test health service or policy interventions across a cluster, they usually cannot be masked to the intervention. Ideally the outcome data collection can be masked to the allocation, but this is not always possible. This means there is a risk of bias as explored below in Section 1.5.2. They may give rise to more ethical issues than individually randomised trials as individuals often do not consent to participate (but rather the institutions or 'cluster' unit). In addition, they can also be challenging to implement, requiring delivery across multiple clusters at the same time. Despite these negatives they remain a viable option in the following circumstances:(Eldridge S, 2012)

- Interventions that are delivered across groups (e.g. education package), which poses the risk of contamination between individuals of a cluster, where subjects intended to be in the control group may inadvertently be exposed to the intervention.
- Interventions that require a change in clinical practice that would be challenging to revert or deliver to some participants and not others (e.g. training on a clinical technique)
- Interventions for which it is not practical or ethical to randomise at the individual level (e.g. new antenatal health system).

- Interventions that impact on outcome measures that are difficult to obtain from individuals but can rely on routine data at the level of the cluster (e.g. maternal mortality).
- Interventions that are costly (e.g. expensive equipment) where it is beneficial to restrict delivery to limited clusters.

An increasingly popular alternative is the stepped wedge cluster RCT (SW-RCT), where all clusters cross from control to intervention in a randomly allocated sequence as shown in Figure 11. Data is collected from the trial start in all clusters and the intervention effect is determined by comparing the data points after delivery of the intervention to those in the control period. All clusters receive the intervention; therefore, this approach is advantageous where there is evidence or belief that the intervention will be of more benefit than harm and therefore it would not be ethical to withhold or withdraw it from some clusters.(Hussey, 2007, Mdege et al., 2011, Brown and Lilford, 2006) It is also preferable when phased implementation is more logical or practical than delivering the intervention simultaneously across clusters. This is usually the case for complex interventions and for trials spread over a wide geographical distance. In addition, the intervention effect is estimated from comparing change between clusters (as in parallel RCTs) but also within clusters. This maximises statistical power and means fewer clusters are required compared to a parallel arm cluster RCT.(Hussey, 2007) This is important when working within the constraints of research funding.

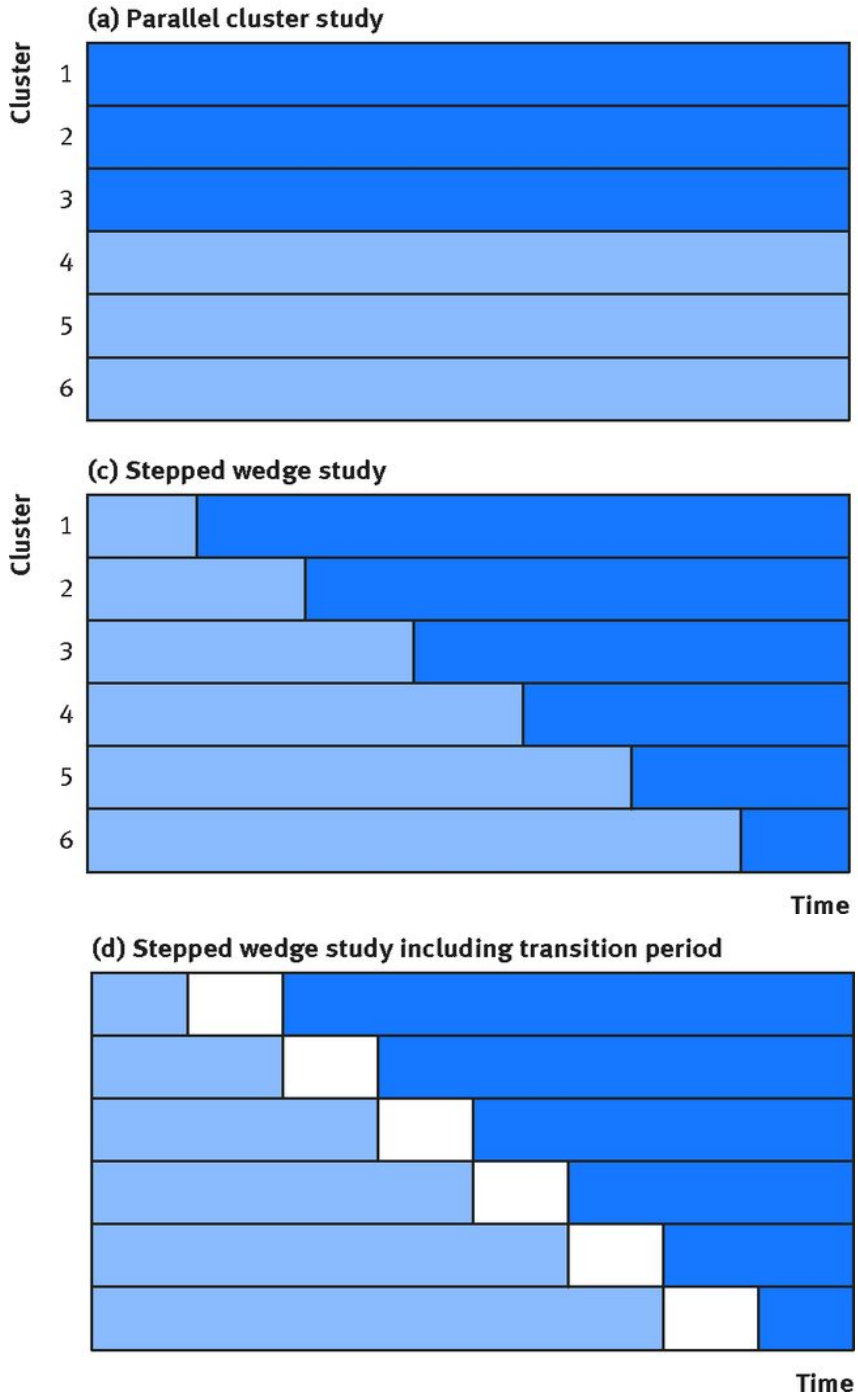


Figure 11 Conventional parallel cluster study compared to stepped wedge cluster randomised controlled trial design. (with and without transition period, described page 56) (Hemming et al., 2015)

Whilst the methods of designing and reporting parallel cluster RCTs are well established,(Schulz et al., 2010) SW-RCT are comparatively newer trial designs. The first SW-RCT was described in 1987,(The Gambia Hepatitis Study Group, 1987) but use has dramatically increased in recent years. A systematic review published in 2006 identified 12 protocols or papers for stepped wedge trials in health care, including both

randomised and non-randomised studies and individual and cluster allocations.(Brown and Lilford, 2006) Each of these twelve studies used a different method of statistical analysis which was frequently incompletely described, with only five of the 12 reporting sample size calculations.(Brown and Lilford, 2006) This systematic review was updated in 2010 and restricted to cluster randomisation, which identified 25 full reports and protocols.(Mdege et al., 2011) Most recently, in 2016 a systematic review identified 60 full reports and protocols, over half of which were published during or after 2013.(Martin et al., 2016) Only 6 of these studies were undertaken in LMIC and all of these in a single country.(Martin et al., 2016) Specific Consolidated Standards of Reporting Trials (CONSORT) SW-RCT guidance is in development;(Hemming K, 2014b) whilst this is awaited these systematic reviews and simulated studies provide valuable guidance as to the best way to design and report SW-RCT and highlight potential challenges of the methodology.

1.5.2 Methodological factors in SW-RCT across multiple countries

Cluster and SW-RCT can reduce potential bias by avoiding individual participant selection (selection bias) and utilising routine data sources. However, the selection of clusters themselves may introduce bias and therefore attention to the selection and recruitment of clusters and facilities within clusters should be reported as well as any that decline after randomisation. Systematic reviews have also identified lack of masking of data collectors as a potential source of bias, when individual participants are identified by those who know the allocation status (measurement bias).(Brown and Lilford, 2006) This is of greatest risk where there are stricter inclusion or exclusion criteria which can be subjectively measured by the data collector. Masking the data collector to the allocation, or if this is not possible, choosing objective outcomes, can reduce this source of bias. Sources of potential bias in cluster RCT are shown in Figure 12.

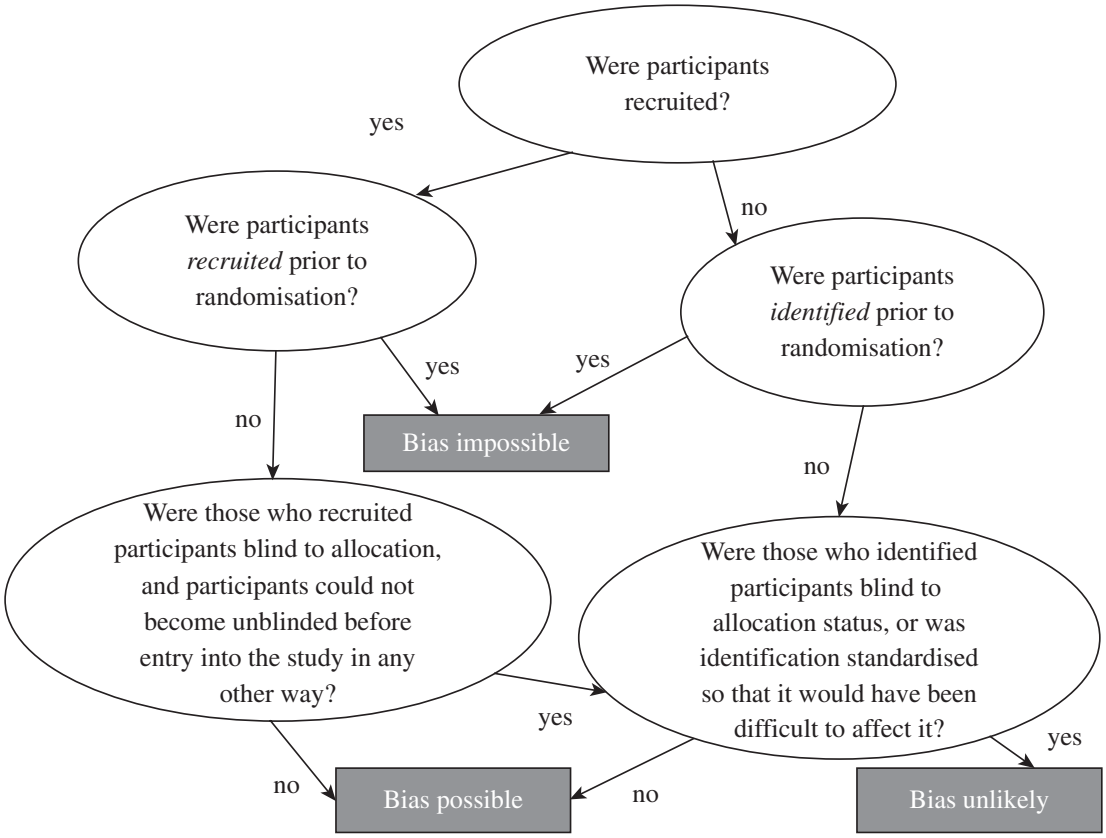


Figure 12 Flow chart to estimate potential bias in cluster randomised controlled trials (Eldridge S, 2012)

As previously mentioned, cluster and SW-RCT also offer more ethical challenges. In an individually randomised trial, the participant consents to be randomised, participate in the intervention and have their data collected. In cluster RCTs, participants are not necessarily aware of and therefore cannot usually consent to randomisation and may not be able to opt out of the intervention and data collection. As they cannot opt out of the intervention (without potentially moving cluster) they cannot provide informed consent.(van der Graaf et al., 2015) Additionally, the HCP delivering the intervention in a certain setting are necessary for any educational or behavioural intervention to be successful and improve care. They therefore can also be viewed as a research participant as they are indirectly affected by the intervention, but they also do not provide consent.(van der Graaf et al., 2015) However, it is the patient that experiences the consequences and therefore the primary outcome of these trials should not be the

change in behaviour of the HCP but the health outcome at the patient level. It is important that these factors are taken into account in any ethics application for a SW-RCT.

The nature of randomising groups to an intervention, means that outcomes for individuals within clusters are likely to be correlated compared to a random sample from the population. Outcomes that are dependent on behaviour, for example a doctor's prescribing practice, are more likely to be similar within a cluster compared to outcomes that are dependent on participants' health, for example BP, which is more likely to be similar between clusters. This 'between cluster variability' is known as intra-cluster correlation (ICC). A small ICC (e.g. 0.01) means that differences between clusters are small as data points are similar. A large ICC (e.g. 0.1) means that differences between clusters are large. Statistical analysis and power calculations for cluster RCTs must take clustering into account because failing to do so can lead to a Type 1 error (showing there is a difference when there is none).(Campbell MJ, 2012) Taking this into account leads to wider confidence intervals, so a larger sample size is required compared to individually randomised trials answering identical research questions. In SW-RCT, as opposed to parallel clusters RCTs, each cluster effectively acts as both control and intervention. This improves the precision of data, so simulated data suggests that SW-RCT are the best design when a large ICC (large differences between clusters) is expected.(Hemming et al., 2015) It also means that individual cluster analysis is possible which can provide interesting secondary analysis. This is important when multiple areas or countries are included, and separate intervention effects are plausible.

Whilst SW-RCT are often chosen to avoid the necessity for simultaneous delivery across clusters, they do require the clusters to be ready to deliver the intervention at the randomly allocated time point. Some designs incorporate a transition period to allow for the time taken for an intervention to embed into a cluster. The cluster is therefore between exposed and not exposed and data from this period is usually not analysed. In

addition, the collection of data over time means that other external changes may occur during the trial period and impact on the outcome or the outcome itself may be subject to baseline trends. For example, if the incidence of a disease decreases over time, independent of the intervention, failure to adjust for this would result in falsely attributing this change to the intervention. This would be true in any trial evaluating maternal mortality as discussed in section 1.2.4. Thus, temporal trends should also be used to inform power calculations for SW-RCT and then estimated and adjusted for in the main analysis.(Hemming et al., 2015) However, this is only possible where there is sufficient data available prior to the trial start.

It is possible that studies undertaken in multiple countries with different populations, health systems and climate would have different temporal trends in different clusters. Only one SW-RCT has been undertaken in multiple European countries,(van der Kooi et al., 2018) which does not contain sufficient methodological detail to determine the relevant methods of analysis. One protocol has been published describing a SW-RCT across three countries in two continents but countries within the study were individually powered.(Canning et al., 2016) Therefore, the effect of different cluster sizes and multiple temporal trends between countries in SW-RCT has not been established.

RCTs can also be described by the extent to which they reflect usual care. Explanatory trials, undertaken in idealised settings, give the intervention the best opportunity to demonstrate effectiveness. However, pragmatic trials, incorporating interventions into usual care, provide more useful information on the likely success of an intervention in a particular group of patients in a particular setting.(Loudon et al., 2015, Treweek and Zwarenstein, 2009) This is known as the external validity, or generalisability of research. Factors that affect external validity are shown Figure 13 on page 82. It cannot be presumed that interventions that are effective in one country, health system, level of care or specific patient group can automatically be applied to others.(Rothwell, 2005) In

addition, many trials use surrogate outcomes, alone or as part of a composite, to measure the effect of an intervention. However, a narrative review published in the Lancet identified that these are often misleading, naming five interventions that were later proven to be ineffective or harmful in large RCTs following initial positive studies using surrogate outcomes.(Rothwell, 2005) It is important that these factors of external validity are taken into consideration in study design and reporting.

Setting of the trial

- Health care system
- Country
- Recruitment from primary, secondary or tertiary care
- Selection of participating centres and clinicians

Selection of patients

- Methods of randomisation
- Eligibility criteria

Characteristics of randomised patients

- Baseline clinical characteristics
- Severity of disease
- Comorbidity

Differences between the trial protocol and routine practice

- Intervention
- Timing of intervention
- Control treatment—intended and actual

Outcome measures and follow-up

- Clinical relevance of outcomes
- Effect of intervention on most relevant components of composite outcomes
- Who measured outcome
- Adequacy of the length of follow-up
- Adverse effects of intervention

Figure 13 Factors that affect external validity of the research results (Rothwell, 2005)

The extent to which research is applicable to its intended use of the results can be measured using the highly cited PRECIS-2 pragmatic trial tool.(Loudon et al., 2015) This identifies nine key domains for pragmatic trial design against which a trial can be scored from one to five. A score of one denotes highly explanatory features (e.g. strict exclusion

criteria, enforced adherence to protocol and single specialised study settings) whereas a score of five denotes highly pragmatic features (e.g. recruitment, eligibility and follow up identical to routine care).(Loudon et al., 2015) Some trials, are more pragmatic by nature due to their intervention and context. For example, trials of low-cost interventions, that pose minimal risk to participants and are applied at a cluster level.(Ford and Norrie, 2016) Pragmatic trial designs are important when the potential benefit of an intervention is great, and the features of a pragmatic trial are feasible and sensible, as the results are of greatest benefit to policy makers. Despite this, there are few published examples of highly pragmatic trials in maternal health in LIC. A study published in 2018 introducing medical supply kits into routine antenatal care with data collected from routine sources in Mozambique, concluded that it is the first of its kind.(Betrán et al., 2018)

1.5.3 Process evaluation of complex interventions

As described above, the methodology of RCTs has changed to allow for evaluation of behavioural or educational (non-pharmacological) interventions which are dependent on participants reacting within a specific context. However, RCTs are often criticized for providing little information about why an intervention worked (or not) and the context within which they were delivered.(Grant et al., 2013, Glasgow et al., 2003) This not only limits their reproducibility, but should an intervention be ineffective, there are no data to suggest how it could be modified.(Munro and Bloor, 2010) In addition, failure to evaluate the delivery of an intervention can result in sound interventions being dismissed due to poor implementation prior to evaluation (Type III error).(Basch et al., 1985) It is therefore important to evaluate not just the efficacy of the intervention but also its implementation (i.e. how it was put to use).(Rabin et al., 2008)

Implementation can be evaluated with a process evaluation. This enables an understanding of what was delivered and how delivery was achieved. The combination of measuring implementation alongside effectiveness has been well described.(Curran

et al., 2012, Peters et al., 2013a) This was in response to the perception that linear progression of research, as shown in Figure 14 on page 84, results in unnecessary delays in changing policy and introducing effective interventions into clinical practice.(Glasgow et al., 2003, Wells, 1999) In low resource settings where the burden of morbidity and mortality is so great, the need for rapid implementation of effective interventions is of even greater importance.

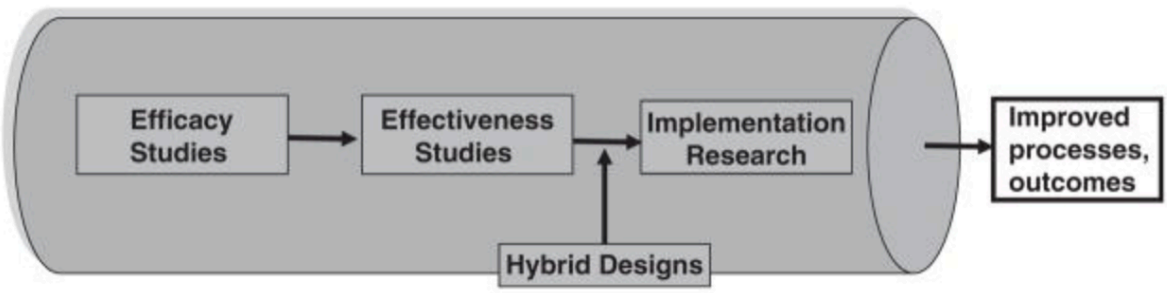


Figure 14 Progression through efficacy, effectiveness and implementation research (Curran et al., 2012)

Curran and colleagues (2012) describe the integration of implementation and effectiveness research as three types of hybrid study as shown in Table 3. Hybrid Type 1 trials that include process evaluations of implementation alongside clinical effectiveness trials are of benefit in exploring important factors such as potential barriers and facilitators to implementation that may inform future scale up, whilst retaining capacity to fully assess the primary outcome. They are most appropriate when the intervention is applicable to new settings or populations and are associated with minimal risk.(Curran et al., 2012)

Table 3 Hybrid design characteristics (Curran et al., 2012)

	Hybrid Trial Type 1	**Hybrid Trial Type 2**	**Hybrid Trial Type 3**
Research Aims	Primary aim is to determine the effectiveness of a clinical intervention. Secondary aim is to further understanding of the context for implementation	Shared primary aim of determining clinical effectiveness alongside testing implementation strategies	Primary aim is to test implementation/ strategy. Secondary aim is to assess clinical outcomes associated with the implementation trial.

The quality and quantity of implementation of an intervention can be measured by a number of variables including:(Moore et al., 2015, Proctor et al., 2011)

- Fidelity – was the intervention delivered in the way originally intended?
- Dose - how much of the original intervention has been delivered?
- Reach/Coverage – how much of the intended population has the intervention reached?
- Adaptation – what changes were made during implementation?
- Acceptability – how acceptable is the intervention to stakeholders?
- Sustainability/Maintenance – how is the intervention maintained or institutionalised?

However, interventions are not just passively received but outcomes occur as a result of participants interacting with them.(Pawson R, 1997) Therefore, process evaluations may also explore potential mechanisms of impact. This can involve measuring variables that the intervention may influence and supporting this with qualitative investigation to explore how and why. This can help to determine how much of the effect is attributable to the

core components of the intervention as opposed to other external factors. Any effect of an intervention is also influenced by the context in which it is delivered, this relates to any external factor which impedes or strengthens its effects, for example the social, cultural, economic and political environment,(Victora et al., 2011) as summarised in Figure 15 on page 86.(Moore et al., 2015) Capturing these factors is of even greater importance when planning studies across multiple different settings.

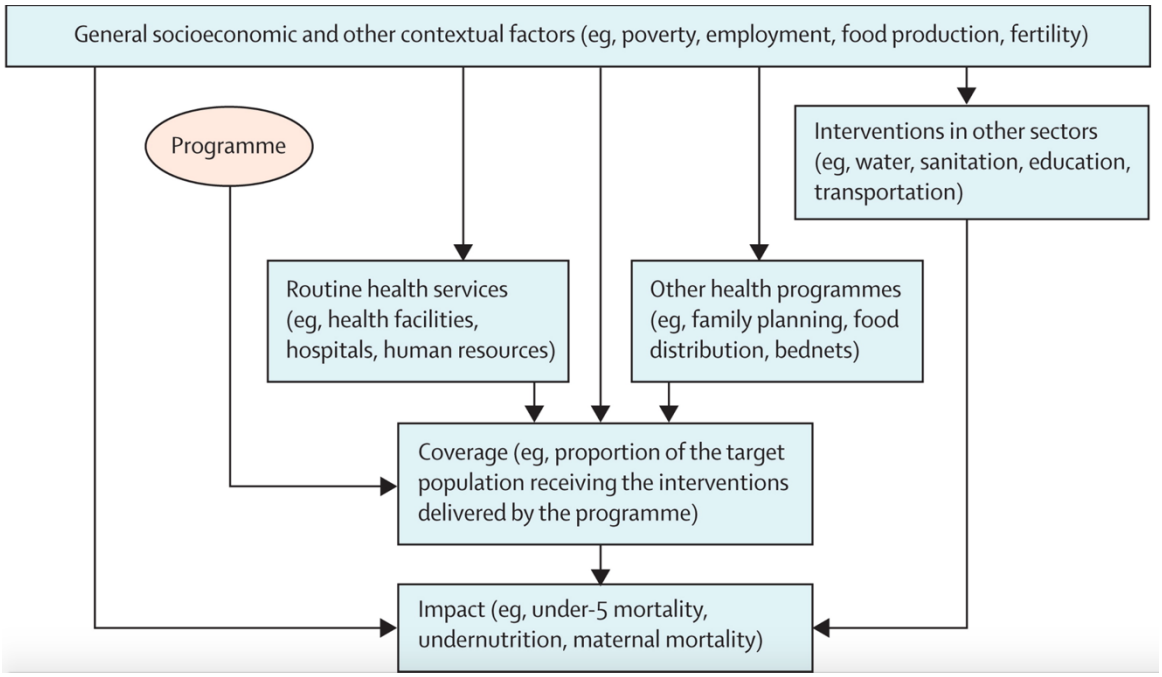


Figure 15 Outline of contextual factors that affect maternal and child health (Victora et al., 2011)

The core functions of a process evaluation therefore include: describing the intervention and exploring ways in which it might work, measuring the quality and quantity of implementation and measuring mechanisms of impact all within a specific context. The interactions of these functions are shown in Figure 16 on page 87.

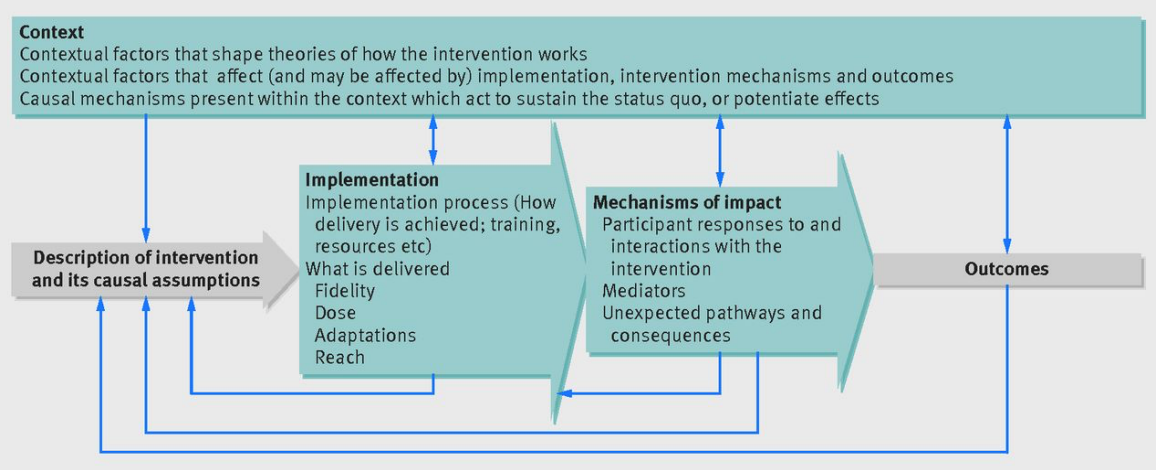


Figure 16 Key functions of process evaluations and relationships amongst them (Moore et al., 2015)

Understanding and describing an intervention and its assumed interactions is a vital first step of planning a high-quality evaluation.(Grant et al., 2013, Michie et al., 2009). Failure to adequately describe the intervention means that others cannot replicate or build on research findings and effective interventions cannot readily be incorporated into practice. The CONSORT specific for trials of non-pharmacological interventions, states that the intervention should be described for each group "with sufficient details to allow replication" with additional details on whether components are standardized and how adherence was assessed or enhanced.(Boutron et al., 2008) Despite this, interventions are often poorly described in published trials. A systematic review of 133 non-pharmacological randomised trials showing that just 39% of interventions were adequately described.(Hoffmann et al., 2013) In 2014, a group of international experts completed a Delphi survey to create a 12 item Template for Intervention Description and Replication (TIDieR) checklist.(Hoffmann et al., 2014) This can be a useful tool to ensure that interventions are fully described, which is important with the growing number of complex interventions that are investigated.

Interventions that contain multiple interacting components, for example the packages of care described in Section 1.4, are often described as complex. However, complexity is also dependent on the following characteristics:(Craig et al., 2008)

- The number and difficulty of behaviours the intervention is aimed at changing;
- The number of groups of organizational levels that the intervention is aimed at;
- The number and variability of outcomes;
- The extent to which the intervention can be adapted.

One way of exploring these characteristics and their interactions is to construct a diagram showing the core components of an intervention, the resources required to deliver it, the activities required to produce change and the intended outcomes. This is known as a logic model. These can take many different forms, a basic example of which is shown in Figure 17 on page 88.(W.K. Kellogg Foundation, 2004)

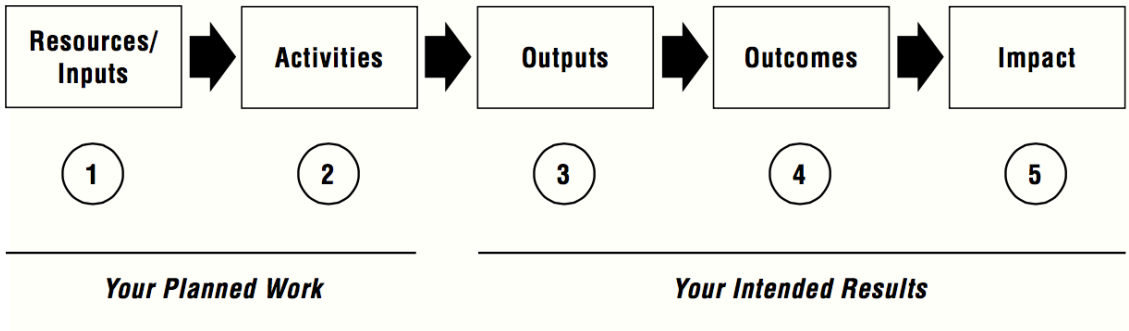


Figure 17 Components of a basic logic model (W.K. Kellogg Foundation, 2004)

In addition to helping to describe the intervention, logic models can help researchers explore the underlying assumptions of an intervention and therefore to understand the key activities and resources required for success.(W.K. Kellogg Foundation, 2004, Moore et al., 2015) An additional purpose of a logic model is to identify which implementation strategies are appropriate. Implementation strategies are methods to enhance the uptake and support of an intervention.(Curran et al., 2012) A review led by the WHO, of both randomised and non-randomised studies of implementation strategies in health services research in LMIC found that multiple strategies are more effective than single strategies but face greater risk of failure. Strategies that increase the number of health workers, including the use of CHWs, was found to be a positive, alongside strengthening accountability, adaptation of strategies to local context, mobilization of resources and stakeholder involvement. However, it was concluded that there was weak

evidence for any particular strategy in one LMIC and even less to suggest that strategies are likely to be the same across countries.(Peters, 2009) More recently, an expert Delphi process generated a consensus on a comprehensive list of 73 implementation strategies, with future plans to rate these for importance and feasibility.(Powell et al., 2015) When designing a trial of a non-pharmacological intervention it is key to consider not just what the intervention is, but how it will be delivered, to whom and the anticipated response. Exploring and defining the implementation strategies can help with this.

Logic models can also be used to determine which measures of implementation are important. Process evaluations are not intended to exhaustively capture every aspect of implementation (Bradley et al., 1999) because it is usually complex and influenced by a wide array external factors that may be changing over time.(Peters et al., 2013b) Instead, they should explore specific questions that are key in understanding the effectiveness of the intervention,(Peters et al., 2013b) as well as measuring key socioeconomic and contextual factors during the trial period.(Victora et al., 2011) It is important to consider the Hawthorne effect, where observation distorts what is delivered, and try to minimise this by collecting only information needed to interpret outcomes, and where possible, from routine data sets.(Moore et al., 2015) Research undertaken in low-resource settings also has to take into account insufficient or low-quality routine data collection, overstretched staff and limited infrastructure. This can make collection of large amounts of detailed data challenging, and therefore this should also be taken into consideration in planning a process evaluation to ensure all measures are feasible and important.

One way of ensuring that data collection is feasible when undertaken across multiple sites and settings with multiple implementing teams is to undertake in depth analysis in selected sites only. This reduces the time and cost of data collection and analysis. However, interventions may have different effects in different contexts and even when the intervention itself is relatively simple, it's mechanism of action may differ.(Moore et

al., 2015) Therefore, evaluating a limited sample of sites may prevent comparison of sites and conclusions from being drawn on the generalisability of the intervention. This is likely to be of greater importance when planning a study across multiple countries.

There are numerous implementation frameworks, models and theories targeted at measuring implementation and guiding this field of research. A systematic review undertaken between 2004-2009 identified a total of 49 implementation frameworks specifically for innovation in healthcare.(Moullin et al., 2015) Frequently these include different stages of implementation, terminology and classification of measures.(Moullin et al., 2015) Only four of these frameworks comprehensively covered a single element of implementation with justifications for their choices.(Kilbourne et al., 2007, Stetler et al., 2011, Lehman et al., 2011, Damschroder et al., 2009) Not only do the majority of frameworks incompletely cover a variety of implementation concepts, they are often developed for a specific innovation, discipline or setting. This means that end-users often select one or more frameworks that partially cover components of their study, potentially missing appropriate oversight.(Moullin et al., 2015) Some of the most cited of frameworks and theories and their focus are summarised in Table 4 on page 91. This is not meant as a comprehensive list but to demonstrate the spectrum of focus and range of guidance available and act as a reference for later studies.

Table 4 Summary of a selection of the most cited frameworks and theories of implementation

Focus of study	Framework or Theory	Summary
Need to understand what is implemented and how  Need to understand quality and quantity of implementation  Need to understand how the intervention works	Normalisation process theory (May and Finch, 2009) and Diffusion of innovation theory (Greenhalgh et al., 2004)	Emphasis on processes by which interventions become fully integrated into their setting
	Steckler and Linnan (Linnan L, 2002)	Implementation measured as fidelity, dose and reach
	RE-AIM framework (Glasgow et al., 1999)	An interventions impact is a result of: Reach, Effectiveness, adoption, implementation and maintenance. Furthers measuring implementation by considering complexity, strategies and responsiveness of participants
	Consolidated framework for Implementation Research (CFIR) (Damschroder et al., 2009)	Five domains of implementation identified: intervention characteristics, outer setting, inner settings, characteristics of individuals and process of implementation. Pragmatic structure to evaluate complex interventions in context.
	Realist Trials (Bonell et al., 2012)	Outcomes are achieved by participants interacting with intervention in a specific context. Context therefore moderates change. Realist evaluation rejects trials and randomisation whereas realist trials advocate testing causal assumptions and contexts that underpin intervention.
	Realistic Evaluation (Pawson R, 1997)	

Efforts have been made to consolidate and simplify multiple frameworks into practical guides, for example, the Medical Research Council (MRC) guidance for process evaluation of complex interventions (Moore et al., 2015) and the WHO practical guide for implementation research in health.(Peters et al., 2013b) These identify that process evaluations can be useful at each stage of evaluating an intervention from intervention design, pilot testing, testing effectiveness and sustainability. During development of an intervention and pilot testing, process evaluations can be useful in exploring how feasible it is to deliver the intervention as planned (fidelity) and how acceptable an intervention is. They can also be useful in identifying how HCP might interact with an intervention to cause a change in behaviour (causal mechanisms).(Moore et al., 2015) Once an intervention has been developed and piloted, a process evaluation can be undertaken alongside a trial measuring effectiveness. The aim is usually to record the quantity and quality of implementation and therefore confirm the internal validity of conclusions on the effectiveness of an intervention. A second aim can be to test causal mechanisms in a larger sample, as understanding how the intervention may work in different settings is important to future scale up. After an intervention is delivered, a process evaluation can focus on how the intervention is sustained and how it could be delivered in new contexts.(Proctor et al., 2015)

Since process evaluations can cover a broad range of aims, the methods and timing of data collection depend on the measures selected. Qualitative research can allow a deeper understanding of the how particular outcomes occur. Quantitative evaluation can allow measurement of implementation and testing causal mechanisms.(Moore et al., 2015, Peters et al., 2013b) For example, the extent to which an educational intervention has been delivered as planned (fidelity) could be quantitatively evaluated by the number of participants trained or qualitatively evaluated by exploring emerging adaptations to the intervention over time. Figure 18 on page 93 shows the commonly used data collection methods for process evaluations.(Moore et al., 2015) The MRC Guidance on complex

interventions suggests that both quantitative and qualitative measures should be integrated to fully understand the intervention and implementation.(Moore et al., 2015) It is also recommended that quantitative process data should be integrated into outcome datasets to explore the effects of implementation on the effectiveness of the intervention.(Moore et al., 2015) However, there is no guidance provided on how to do this and examples that integrate these measures are vague.

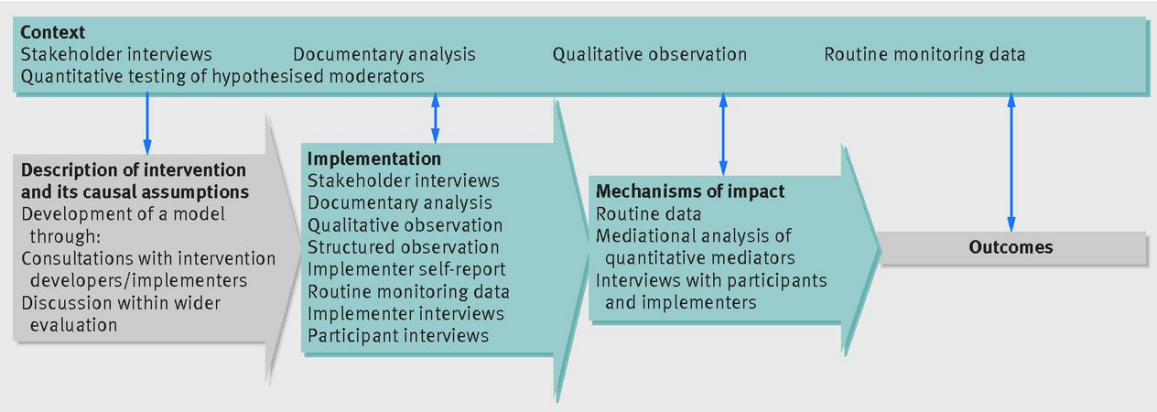


Figure 18 Commonly used data collection methods for process evaluations (Moore et al., 2015)

There are several examples of implementation research for the purpose of intervention development (Norris et al., 2016, Bua et al., 2015, Hirschhorn et al., 2015, Kung'u et al., 2018) or to inform implementation of proven effective interventions (Bergh et al., 2005, Kung'u et al., 2018, Bergh et al., 2014, Maru et al., 2018, Das et al., 2018) in maternal health in LMIC. However, despite the clear merits of measuring implementation alongside effectiveness, there are limited examples of hybrid studies, or parallel process evaluations in LIC, especially in maternal health, where timely scale up of effective interventions can save lives. Therefore, examples of how to integrate implementation and effectiveness measures are scarce. Systematically reviewing the literature in this field is challenging due to the varied terminology and multitude of frameworks used.(Colquhoun et al., 2014) A cross-sectional review of 581 articles on knowledge translation or implementation identified 100 different terms to describe this field.(McKibbon et al., 2010) In addition, studies that do undertake evaluation of both

areas rarely explicitly acknowledge this, as specific guidance on how to undertake joint evaluation has only emerged in recent years (Curran et al., 2012, Moore et al., 2015, Craig et al., 2008) and the varied methodologies rarely fit into the remit of one manuscript or journal.

Two published studies undertaking joint evaluation could be found. One was nested within a cluster RCT of a systems-engineering approach in preventing mother-to-child-transmission of HIV in Mozambique, Kenya and Cote d'Ivoire. It assessed fidelity and then used the Consolidated framework for Implementation Research to guide qualitative work in order to determine the core components of the intervention and identify which implementation measures were associated with successful delivery of the intervention. This was done by rating each measure for one high performing and one low performing facility in each country. As trial outcomes were not available at the time of evaluation, performance of sites was determined by fidelity.(Gimbel et al., 2016) This was subjectively measured, based on research staff experience, and this study is limited by the restriction to only qualitative evaluation. This limits the applicability of the results. It is therefore important that trials include both quantitative and qualitative measures to fully understand an intervention.

Another published SW-RCT in maternity care states that a process evaluation is planned but with no detail provided.(Chavane et al., 2014, Betrán et al., 2018) An additional five protocols were found, only one of which had a clinical primary outcome as opposed to a process measure or behaviour change outcome and all but one of which were undertaken in a single country (Table 5). None of the studies are reported yet and none of the protocols give detailed analysis plans for the integration of qualitative and quantitative or how they will be integrated with health outcomes. These examples highlight the scarcity of literature in the field and lack of standardised approaches.

Table 5 Hybrid studies in maternal health exploring implementation alongside health-related outcomes

Study design	Study setting	Intervention	Primary Outcome	Implementation measure	Method	Integration of outcomes
SW-RCT (Chavane et al., 2014, Betrán et al., 2018)	Mozambique	Medical supply kits	Quality of antenatal care	Not described	Not described	Not described
Hybrid effectiveness cluster-RCT (Utz et al., 2017)	Morocco	Fasting glucose test at first ANC with nutritional counselling	Birthweight	Adoption and feasibility	Mixed methods	Not described
Individual RCT (Ridgeway et al., 2015)	USA	Antenatal care model	Patient Satisfaction	Reach, effectiveness, adoption and implementation (RE-AIM)	Mixed methods	Qualitative data on patient satisfaction, implementation and use of the intervention will be compared with effectiveness
Hybrid Type 2 cluster-RCT(Kikuchi et al., 2015)	Ghana	Continuity of care intervention package	Continuity of care and its documentation	Acceptability, coverage, adoption, fidelity, cost, sustainability	Mixed-methods	Not described
Hybrid Type 2 non-randomised cluster role out (Maru et al., 2018)	Nepal	CHW delivering integrated maternal, newborn package	Institutional birth rate	Reach, Efficacy, Adoption, Implementation, Maintenance	Mixed-methods	Generalized estimating equations to show correlation. Integration not described.
SW-RCT (Canning et al., 2016)	Sri-Lanka, Tanzania, Nepal	Post-partum contraceptive intrauterine device services	Percentage uptake	Dose, potential mediators, patient satisfaction, sustainability	Mixed-methods	Iterative comparison of mixed-method results

In order to interpret and maximise the use of process evaluations it is important to be able to quantify implementation success and relate this to effectiveness. This is especially important when examining an intervention across multiple contexts where different effects may be seen in different sites. None of the above protocols or papers describe integration of quantitative process and clinical outcome measures or define what would be deemed successful implementation.

In other specialities of research, such as education and health promotion, the impact of implementation on effectiveness outcomes is better established. In 2008, Durlak and DuPre undertook a systematic review of the influence of implementation on program outcomes. From five meta-analyses (including 483 studies including interventions on anti-bullying programs, drug prevention and school aggression) and 59 additional studies, they concluded that higher implementation fidelity and/or dose are associated with better outcomes.(Durlak and DuPre, 2008) However, the meta-analyses were limited by the quality of original data with actual level of implementation being infrequently reported and instead reliance on author reported implementation. They describe two methods of integrating clinical and implementation data:(Durlak and DuPre, 2008)

- Categorical analysis: comparing outcomes between groups with high implementation to those with low implementation.
- Continuous analysis: correlating outcomes with continuous variables for example percentages to assess fidelity.

They reported that both strategies found a relationship between implementation and outcomes, with 76% reporting significance for at least half of their program outcomes, but that the latter method achieved greater statistical power. However, the majority of these 59 studies reported only one aspect of implementation, usually fidelity (69%),(Durlak and DuPre, 2008) which was determined by behavioural observation or self-reported and thus subject to bias. Where possible trials should aim to collect

information on amount of intervention delivered (dose) and the extent to which the target population is reached (reach), as they are also critical in determining the success of an intervention. Objective measures should be chosen to reduce bias.

A more recent narrative review of methods to measure implementation strength across all specialities included 26 studies, all of which were undertaken in a single country, six being LIC. They reported that many studies combine implementation measures for analysis and most studies score individual measures as well as average them across implementation domains and overall. However, only two studies then linked implementation levels with study outcomes, one which correlated implementation score with immunisation coverage in Northern Sudan,(Ryman et al., 2011) and the other which correlated level of implementation with change in physical activity.(Wilson et al., 2010) The key features of these studies, and three others not included in the review that utilise different methodology to measure implementation strength and compare with other outcomes, are shown in Table 6 on page 98. Each describe a different method of combining process and effectiveness outcomes with the justification for this method being poorly or rarely described. The terminology used to describe the implementation measures differs in each paper.

Table 6 Example of studies that integrate implementation and outcome measures

Study	**Study design**	**Study setting**	**Intervention**	**Implementation measure**	**Method of data collection**	**Method of scoring**	**Integration of implementation score and outcome**
Health extension worker programme, Ethiopia (Karim et al., 2013)	Non-experimental before and after comparison	101 districts in Ethiopia	Training of health extension workers in essential newborn care	Four measures of dose and reach e.g. % of women reporting household visits by health extension worker	Interview surveys with mothers at baseline and 2 years	Each area assigned an overall score (sum of the four measures). Scores calibrated between 0-10. Internal validity of measures defined.	Dose-response relationships tested using regression. Controlling for secular trend, respondents' characteristics, and community-level factors.
Affordable Medicines Facility, Global Fund (Ng et al., 2011)	Non-experimental before and after comparison	Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda and Tanzania	National programmes designed to increase access and use of quality anti-malarials.	Two measures of duration e.g. number of months drugs available. Two measures of exposure e.g. proportion of HCP trained.	Surveys at baseline and endpoint from stockists. Key informant interviews	Percentage change	No formal statistical association undertaken. Description of how implementation strength mirrored performance.
Reaching every district strategy for routine immunization (Ryman et al., 2011).	Non-experimental before and after comparison	70 localities of Northern Sudan	Five strategies to plan, implement and monitor immunization services	Multiple measures of fidelity, dose and reach e.g. number of visits and reports, quality of records,	Standardised work sheets, semi structured interviews in four selected districts, data review	Performance indicators scored 0-10. Individual components assigned weight and averaged into component scores then summed for each locality.	Implementation scores from two high performing and two low performing localities correlated with immunisation coverage. Incomplete contextual data so not included in analysis

				equipment functioning.			
Workplace trial to increase physical activity (Wilson et al., 2010)	Cluster randomised-controlled trial	16 matched pairs of retail organization sites in USA and Canada. Random allocation.	Individual and team goal setting and environmental supports to increase physical activity	measures of fidelity e.g. % of participants given manual; dose delivered e.g. % that met as a team; and dose received e.g. % reporting manual was helpful	Surveys from participants, implementer reports	Sites ranked from highest to lowest based on four aspects of survey responses. The four rankings were averaged to give an overall rank for each site. Sites and participants split into groups by median.	Latent growth modelling used to test the difference in change in physical activity in high and low implementation sites.
Rational prescribing in primary care (Fretheim et al., 2006)	Cluster randomised-controlled trial	146 general practices in Norway	A multifaceted intervention for improving guideline adherence for pharmacological management	Recipient readiness (adoption), fidelity and reach e.g. length and attendance of educational meeting, Reach e.g. proportion of cases with risk assessments	Questionnaires, semi structured interviews and routine data extracted from electronic medical records	Individual variables not score	Initial univariate regression to explore association between potential explanatory variables and variation in outcomes. Then multivariate regression analyses of predictive for each of the three main outcomes in each practice.

Overall, stepped-wedge and cluster trials are increasing in popularity as ways of testing the effectiveness of complex interventions. The importance of measuring implementation alongside effectiveness is now largely recognised and a wide range of guidance now exists. This methodology is likely to be of great benefit for research in LIC, where reducing the time taken for effective interventions to be incorporated into routine care and identifying which components of an intervention are essential to influence the outcome is key. Trials of complex interventions should aim to measure sufficient implementation outcomes to be able to fully describe the delivery of the intervention, the context in which it was delivered and how it had an effect. To be comprehensive this will usually require mixed-methods, which can be integrated to further understanding. These results can be used to explain the effect of the intervention on clinical outcomes, although few trials have achieved this, especially in LIC in maternity care. This rigorous data can help to explain the quality and quantity of intervention delivery (and therefore the extent to which results are valid), the way an intervention worked in a particular setting (and therefore how it could be delivered to other settings) or if an invention did not work the reasons why (and therefore how it could be modified and changed).

1.5.4 Statement of the Problem

Reducing maternal mortality and morbidity remains high on the agenda of international global health. There are proven, effective interventions but many barriers exist in ensuring that women have access to them. All these interventions require timely administering in order to save lives. Early detection of pregnancy complications is therefore the first critical step in saving lives. There are known risk factors for the most common pregnancy complications, haemorrhage, sepsis and hypertension, but prediction of clinical outcome remains limited. Therefore, monitoring of vital signs is essential. This requires sufficient access to reliable equipment, staff trained to use it, and capacity to respond to abnormal results. There is evidence that training HCP and using EWS can improve maternal care but very few studies have evaluated their impact on

health outcomes, especially in low resource settings where they have the greatest capacity to work. Therefore, there is a need for robust evidence on the efficacy of interventions aiming to reduce morbidity and mortality by measuring vital signs to diagnose a complication and triggering appropriate action pathways.

1.5.5 Rationale for the CRADLE Trial

It is on the basis of this problem that the CRADLE trial was developed. The CRADLE VSA, as described in Section 1.4.5, is a novel solution to this problem. This first iteration of this device (Microlife 3AS1-2) was first developed in 2006 and validated as accurate in a non-pregnant adult population (Figure 19).(de Greeff et al., 2008) In 2012 it was then validated as accurate in pregnant women, including women with pre-eclampsia (Nathan et al., 2015b) and women with low BP.(Nathan et al., 2015a) The CRADLE-1 study was funded in 2013. This preliminary field work identified that over 90% of health clinics in a rural district in Tanzania did not have access to a working BP device. The prototype device was introduced into facilities and a tally counter used to monitor use. This confirmed that the device was used frequently. A further before and after study was undertaken in three rural hospitals in Tanzania, Zimbabwe and Zambia. This study demonstrated that delivering devices to 20 antenatal clinics that refer to each of the three hospitals resulted in a decrease in the proportion of women who had never had their BP measured in pregnancy (n=1241, 25.1% preintervention to 16.9% postintervention, OR 0.58, 95% CI 0.42-0.79).(Nathan, 2018)

Funding for the CRADLE-2 study was achieved to further test and improve the device. Questionnaires (n=88) were used across a variety of clinical settings in India, the UK and Canada to explore understanding of the visual display. This, in combination with retrospective analysis of vital signs in women with PPH (as described in 1.4.2 (Nathan et al., 2015c, El Ayadi et al., 2016)) resulted in creation of the new CRADLE VSA model with the EWS traffic light alert (Figure 19). A 15-month prospective validation of the

thresholds of the EWS was undertaken in 2015 to 2016 in three tertiary hospitals in South Africa. This demonstrated that in women with obstetric haemorrhage and sepsis the traffic light threshold strongly predicted risk of ICU admission and emergency hysterectomy.(Nathan, 2018) In women with hypertension, the threshold predicted risk of renal impairment, ICU admission and magnesium sulfate use.(Nathan et al., 2018b) Qualitative work undertaken in India, Mozambique, Nigeria and South Africa (n=155 interviews and n=6 focus groups) demonstrated that HCP found the device easy to use and found the traffic lights improved confidence in decision-making.(Nathan et al., 2018a)

These early studies demonstrated the need for reliable equipment in the community, the acceptability of the device and potential benefit of the traffic light alert in predicting adverse maternal outcomes. Whilst the validity of the CRADLE VSA as an accurate, easy to use tool is confirmed, the potential impact of the device on routine maternity care and resulting clinical outcomes is unknown. The CRADLE-3 trial therefore aims to determine whether introduction of the device into routine maternity care could reduce morbidity and mortality. If proven to be effective, the result would support wide scale implementation. Simultaneous evaluation of implementation would provide vital information on the context, resources and delivery of the intervention required for scale up to be successful.

Figure 19 Earlier model Microlife 3AS1-2 and the final CRADLE Vital Signs Alert

It is hypothesised that the intervention will reduce morbidity and mortality by the following steps:

- Training

This includes formal task-sharing where CHWs are an integral part of routine maternity care and informal task-sharing where other cadres of HCP routinely monitor vital signs. It is hypothesised that this will improve number of staff able to measure vital signs accurately and the capacity of staff to recognise abnormal results and initiate appropriate action. Therefore, more women will have more monitoring and problems will be detected earlier.

- Availability of equipment

Increasing the availability of reliable vital signs equipment will increase the efficiency of HCP and physical capacity to monitor vital signs thus improving access for women to receive monitoring.

- Early warning system

The EWS will act as an alert to all HCP highlighting the need for action. This will increase the confidence of HCP to trigger action and reduce delays in diagnosing pregnancy complications by all cadres of HCP.

- Perceived quality of care

The training of staff and availability of equipment may result in improved perception of quality of care and therefore the likelihood of women attending healthcare.

This intervention is complex because it is anticipated to work across multiple levels of care with a wide variety of HCP in multiple different contexts. It also requires a change in behaviour of HCP to increase the number of women that are monitored, the frequency of monitoring and the time taken for action. Therefore, the success of the intervention is dependent on capacity to change behaviour, in addition to the response of women. These interactions within the wider determinants of health are shown in Figure 20 on page 105.

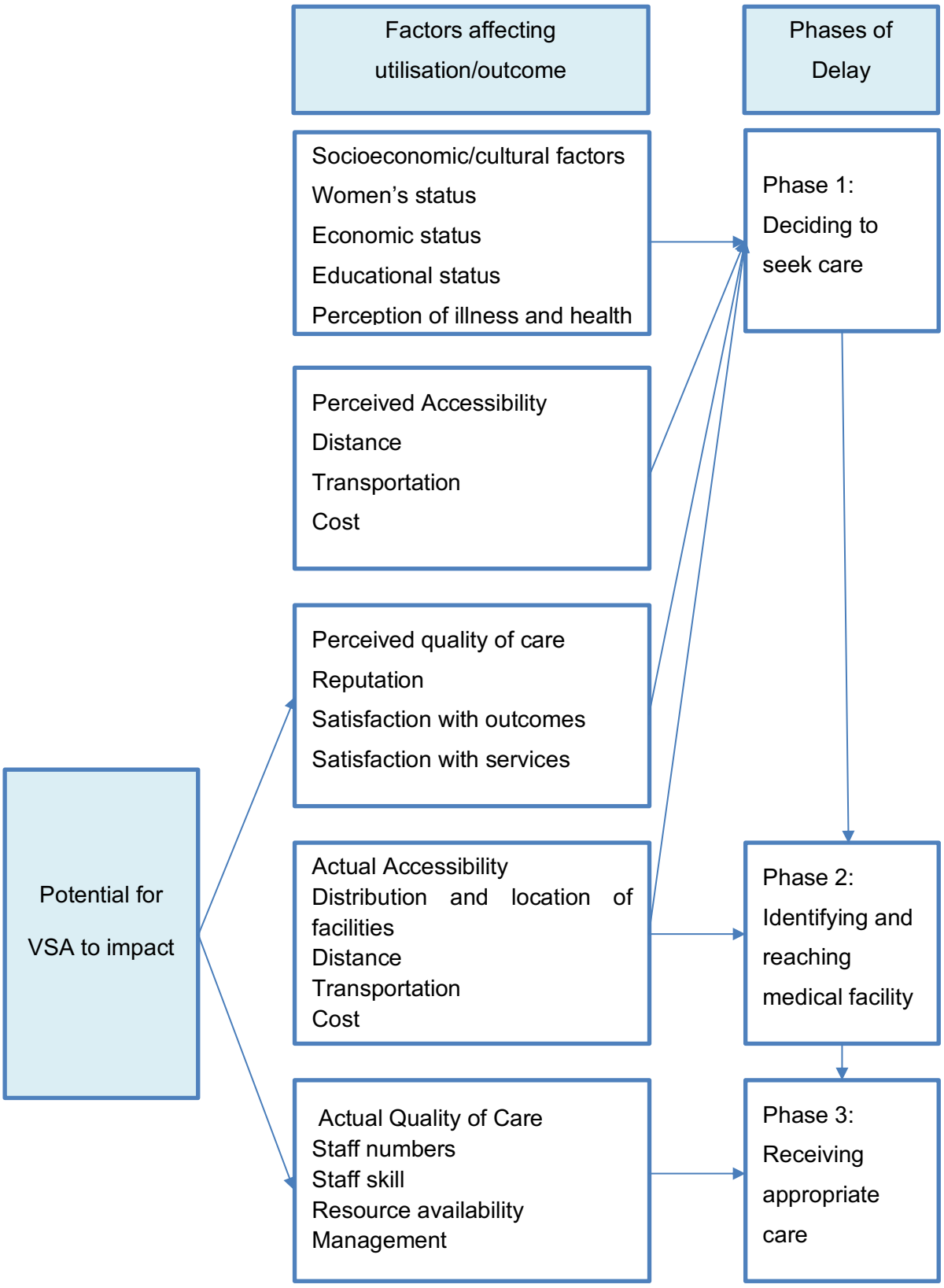


Figure 20 Potential interaction of CRADLE intervention on phases of delay (Thaddeus and Maine, 1994)

As the potential benefit of the intervention is applicable in any setting it was agreed by the project team to include a wide number of geographical settings. Experiences from CRADLE 1 and 2 demonstrated the need for the VSA to be introduced into a health care system with an existing referral system and some capacity to respond to abnormal vital signs. It was a requirement of the funding that sites be linked with an academic institution or non-governmental organisation and also necessary to ensure there was suffiient infrastructure to deliver the research to international standards. Sites were therefore identified through discussion with our stakeholders and partners involved in CRADLE 1 and 2. All sites approached agreed to be involved.

Given the complexity of the intervention the evaluation has been informed by the MRC guidance for complex interventions. The testing will commence with a feasibility study to test the acceptability and feasibility of the CRADLE intervention components and the methods of implementing. The hypothesis above will be explored with stakeholders in the development of a logic model. The results of the feasibility study will be used to refine the protocol and develop the protocol for the process evaluation, which will measure key components of implementation across all sites.

The main trial will be a pragmatic SW-RCT. This trial design has been chosen because vital signs measurement is a key component of routine antenatal care. Health facilities in LIC often have inadequate access to equipment (as described in Section 1.4.3) therefore individual randomisation would not be ethical or feasible. A parallel cluster design could have been used but given the possible positive impact of the intervention and desirability of providing this equipment (even if efficacy in reducing morbidity and mortality is not shown), it is preferable to deliver it to all clusters. Simultaneous delivery across clusters in different countries would have been challenging and stepped implementation represents a practical solution. As the trial is being undertaken in multiple LIC this design also allows analysis of individual clusters with the period before the

intervention effectively being the control for each cluster. This will enable an understanding of whether the intervention worked in different contexts. Whilst this methodology is increasingly popular (as described in Section 1.5.1) there are currently no SW-RCT undertaken across multiple LMIC. Therefore, this will produce novel findings on the suitability of this methodology and its challenges.

As this is a trial of a low-cost intervention, that pose minimal risks to participants and are applied at a cluster level into routine maternity care, with no change to the organisation of care, it is inherently pragmatic in many ways. However, effort was made to ensure the methodology was as pragmatic as possible to increase the external validity of the results, and therefore suitability for scale up, should the intervention be successful. Figure 21 shows the PRECIS-2 tool completed for the CRADLE Trial. The primary outcomes will be collected from routine patient records with no exclusion criteria, no additional participant recruitment and they will be directly relevant to participants. The settings for the trial were purposely selected and represent a balance between pragmatic application to all levels of routine maternity care, and restriction to services with recognized referral patterns in place. The two PRECIS-2 domains that are less pragmatic is the flexibility in adherence to the intervention and follow up. The CRADLE VSA will be incorporated into usual care and existing alternative BP devices will be requested to be secured out of use once HCP are orientated with the CRADLE VSA. Ongoing support to HCP in the use of the CRADLE VSA will be provided by the implementation team.

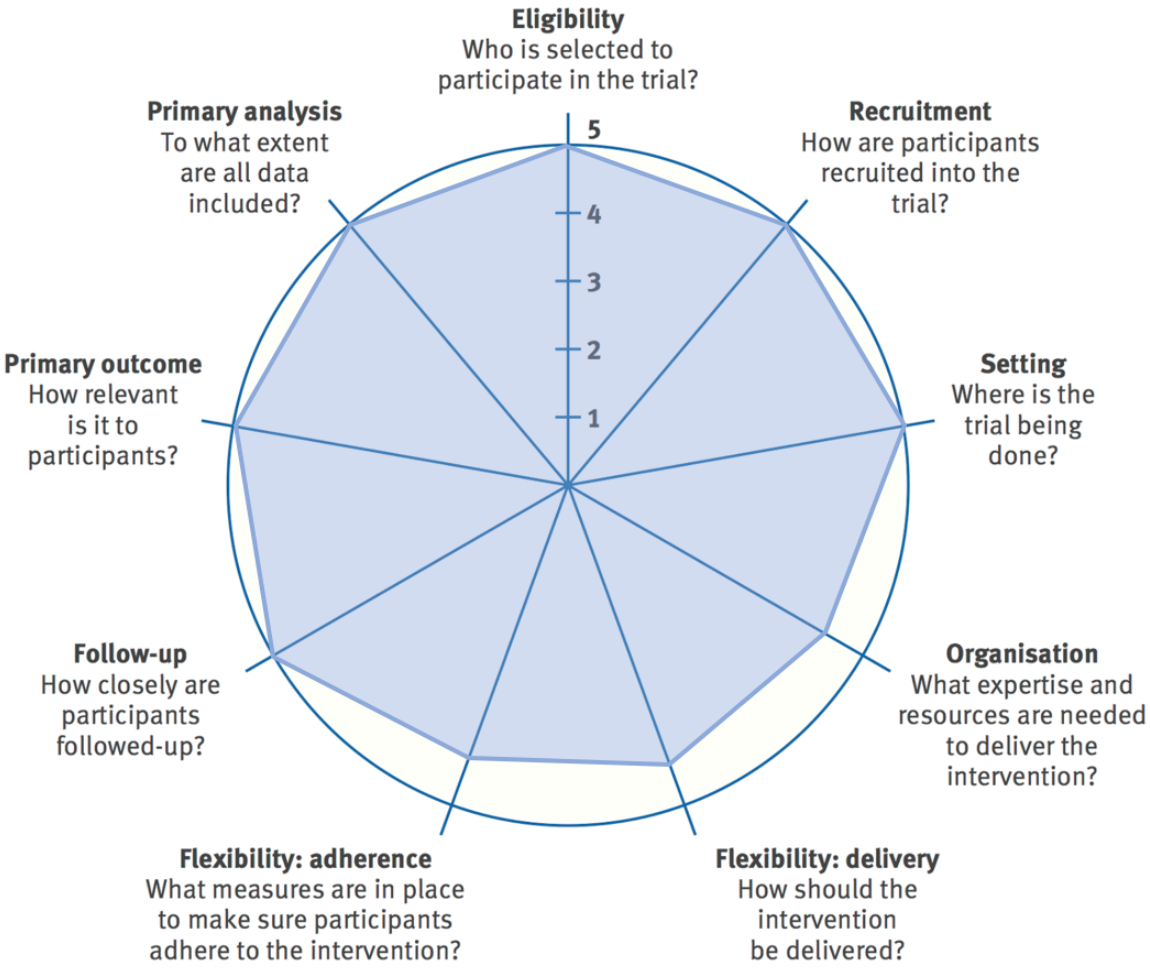


Figure 21 PRECS-2 Tool completed for the CRADLE Trial (Loudon et al., 2015)

The primary outcome is to evaluate the impact of the intervention on morbidity and mortality. This has been chosen over intermediate process outcomes, such as changes to clinical management, because surrogate outcomes do not always correlate with the intended health outcomes. In addition, demonstrating a successful change in an important health outcome is most likely to result in the intervention being incorporated into policy. Given the challenges of collecting data from routine sources in LIC with limited infrastructure, it will be necessary for outcomes to be unequivocal and not dependent on availability of diagnostic services. This will also reduce measurement bias as women, HCP and data collection cannot be blinded to the intervention.

As implementation across multiple clusters has the capacity to differ and impact on the effectiveness of the intervention, evaluation of the implementation process is vital. As this is a secondary outcome of the trial this is a hybrid type 1 evaluation. The measures of implementation will be determined during the feasibility study. Simultaneous evaluation is preferable within the time and cost constraints of the funding period. Mixed-methods will be used to fully explore implementation and potential mechanisms of action in each context. The results will be used to understand the health outcomes. Despite this being a recommendation, there are no published, robust process evaluations undertaken alongside trials of effectiveness of maternal health interventions in LMIC. Therefore, this will also provide new knowledge of methodologies.

Evidence regarding the prevalence of the key causes of maternal mortality and morbidity is primarily based on modelled data from observational studies based in hospitals or household surveys that are prone to bias. There is a lack of prospective, rigorously collected prevalence data across the health system. It is anticipated that the data of this trial will provide some of the largest cohorts of maternal morbidity and mortality worldwide. Therefore, the potential for secondary analysis will be explored once the final components of the outcomes are known.

1.6 Aims and Objectives of this thesis

This thesis aims to evaluate the impact of a novel vital sign device and educational package on maternal mortality and morbidity in LMIC. Specific objectives of this thesis are as follows:

1. To determine the acceptability of the CRADLE intervention components and the feasibility of its implementation and methods of evaluation and to use the results to refine the intervention and protocol of the main trial and process evaluation (Chapter 2).

2. To test the effectiveness of the CRADLE intervention in reducing maternal morbidity and mortality in LMIC settings (Chapter 3).
3. To evaluate the implementation of the CRADLE intervention in order to understand the results and its potential impact (Chapter 4).
4. To use the data to explore the incidence of eclampsia and morbidity from HDP, in relation to magnesium sulfate availability (Chapter 5).

2 Evaluation of a novel vital sign device to reduce maternal mortality and morbidity in low-resource settings: a mixed method feasibility study for the CRADLE-3 trial.

2.1 Abstract

Background:

The CRADLE-3 trial is a stepped-wedge RCT aiming to reduce maternal mortality and morbidity by implementing a novel vital sign device (CRADLE VSA) and training package into routine maternity care in 10 LIC. The MRC Guidance on complex interventions proposes that interventions and implementation strategies be shaped by early phase piloting and development work. We present the findings of a three-month mixed-methodology feasibility study for this trial and describe how this was informed by the MRC guidance and how the results were used to refine the study design.

Methods:

The fidelity, dose, feasibility and acceptability of implementation and training materials were assessed in three representative non-trial sites (Zimbabwe, Ethiopia, India) using multiple-choice questionnaires, evaluation of clinical management (action log), HCP semi-structured interviews and focus groups 4-10 weeks after implementation. Simultaneously, the 10 sites included in the main trial (eight countries) collected primary outcome data to inform the power calculation and randomisation allocation and assess the feasibility of data collection.

Results:

The package was implemented with high fidelity (85% of HCP trained, n=204). The questionnaires indicated a good understanding of device use with 75% of participants scoring >75% (n=97; 90% of those distributed). Action logs were inconsistently completed but indicated that the majority of HCP responded appropriately to abnormal

results. From 18 HCP interviews and two focus groups it was widely reported that the intervention improved capacity to make clinical decisions, escalate care and make appropriate referrals. Nine of the ten main trial sites achieved ethical approval for pilot data collection. Intensive care was an inconsistent marker of morbidity and stroke an infrequent outcome and therefore they were removed from the main trial composite outcome. Tools and methods of data collection were optimised, and event rates used to inform randomisation.

Conclusions:

This feasibility study demonstrates that the components of the intervention were acceptable, methods of implementing were successful, and the main trial design would be feasible. Qualitative work identified key moderators that informed the main trial process evaluation. Changes to the training package, implementation strategy, study design and processes were identified to refine the implementation in the main trial.

Trial registration: ISRCTN41244132; Registered 24/11/2015.

2.2 Background

Maternal mortality remains a challenge in the post-MDG era, especially in low resource settings where in 2015, 800 women died every day from complications of pregnancy and childbirth.(World Health Organisation, 2015b) The most common causes of maternal mortality worldwide are hypertensive disorders, obstetric haemorrhage, sepsis and abortion complications. There are simple interventions that are readily available to treat these conditions. However, in low-resource settings, delays in presenting to care, reaching care and receiving this care all contribute to high maternal mortality. Measurement of vital signs is the first step in recognising women at risk of deterioration and therefore in initiating life-saving treatments.(World Health Organisation, 2005a) Despite this, access to accurate equipment to measure vital signs and adequate HCP training on escalation pathways are frequently lacking in LMIC.(Baker et al., 2012)

The CRADLE-3 trial aims to determine whether implementation of a novel vital sign device and educational package into routine maternity care at both community and facility levels, will reduce a composite outcome of maternal mortality and morbidity in LMIC. This is a stepped wedge RCT based in eight LMIC over 20 months. The CRADLE VSA is a semi-automated device that measures BP, pulse and calculates the mother's risk of shock. It has been extensively validated for accuracy(Nathan et al., 2015b, Nathan et al., 2015a) and usability(Nathan et al., 2018a) and the need defined in this context through field work and stakeholder engagement.

The trial development was informed by the MRC guidance for complex interventions.(Craig et al., 2008) Although the stages of development and evaluation can take many different forms, it is recommended that key uncertainties in the design are systematically studied in a development phase. Procedures should be tested for their acceptability and the likely rates of recruitment estimated to inform sample size calculations. The guidance also states that a mixture of qualitative and quantitative methods is likely to be needed in order to understand barriers to participation and estimated responses. Guidance on how best to undertake this was provided by Moore et al. in 2015.(Moore et al., 2015)

Whilst the MRC guidance is heavily cited there are few published papers that consider its practical application during this stage especially taking into context the challenges of working in multiple LMIC. Prior to the CRADLE 3 trial start a mixed-methodology feasibility study was undertaken to finalise the intervention and implementation processes which were guided by the Expert Recommendations for Implementing Change (ERIC) project.(Powell et al., 2015) Potential causal mechanisms and contextual factors that may influence the success of the trial were also identified. A logic model was created to describe these components and to identify the key research questions that

inform the process evaluation of the main trial.(W.K. Kellogg Foundation, 2004) Through presenting results of this feasibility study, we aim to provide a worked example of the application of the MRC guidance in finalising the subsequent trial protocol and process evaluation.

2.3 Method

The study took place over three months from November 2015 to January 2016 with a further three months to analyse and adapt the intervention and protocol prior to the trial start in April 2016. It consisted of three key objectives:

1. Exploration of the acceptability and feasibility of the CRADLE programme components and the development of its implementation strategies by a mixed-method evaluation in three non-trial sites representative of the 10 main trial clusters.
2. Collection of primary outcome data in the 10 main trial clusters in order to evaluate the methods of data collection, and assess factors related to the randomisation programme (number of deliveries per month) and the sample size calculation.
3. Utilise results to optimise final CRADLE 3 protocol including training materials and implementation strategy for main trial.

Setting

Implementation was undertaken in three areas representative of the main trial clusters. These were a convenience sample of facilities meeting the study's inclusion criteria but geographically distant to avoid contamination of the main trial. All facilities approached agreed to participate. These were sites based around Ramadurg in Karnataka, India, Bishoftu in Ethiopia, and Masvingo in Zimbabwe. In accordance with the 10 main trial clusters (list in Appendix 7.1) these included one or more secondary or tertiary facilities

that provided comprehensive emergency obstetric care and the surrounding primary care facilities that referred to these higher facilities and were urban or semi-urban.

Participants

The CRADLE VSA was incorporated into routine maternity care. All HCPs working in these services were eligible for training and all women identified as pregnant or within the six weeks post-partum period, presenting for antenatal, intrapartum or postpartum care within the three areas were eligible for inclusion.

Intervention

The intervention, described in accordance with the TIDieR guidance,(Hoffmann et al., 2014) included two key components. The Microlife CRADLE VSA is a novel device that accurately measures BP and pulse(de Greeff et al., 2008, Nathan et al., 2015b, Nathan et al., 2015a) and calculates the pregnant mother's risk of hypovolaemic or septic shock.(Nathan et al., 2015c, El Ayadi et al., 2016) It has been specifically developed to meet the WHO's criteria for use in a low resource setting. A traffic light EWS display alerts users to abnormalities in the vital signs results. The lights are triggered by standard thresholds of hypertension as well as by SI,(Nathan et al., 2015c) as shown in Table 7. The CRADLE VSA was incorporated into routine maternity care.

Table 7 Thresholds that trigger the CRADLE VSA Early Warning System

Hypertension Thresholds		
Light and Arrow Results	Category	Blood Pressure (mmHg)
RED LIGHT UP ARROW	Severe hypertension	≥ 160 and / or≥ 110
YELLOW LIGHT UP ARROW	Hypertension	≥ 140 & ≤ 159 and / or ≥ 90 & ≤ 109
GREEN LIGHT	Normal	< 140 and< 90
SI Thresholds		
Light and Arrow Results	Category	SI
RED LIGHT DOWN ARROW	Severe shock	≥ 1.7
YELLOW LIGHT DOWN ARROW	Shock	≥ 0.9 and <1.7
GREEN LIGHT	Normal	< 0.9

Primary, secondary and tertiary facilities were allocated devices according to their delivery rate, staffing numbers and number of beds per ward. Pre-existing BP devices were removed from clinical areas, unless existing equipment has functionality designed for that area e.g. repeated automated measures in a high dependency area. This was supported with a CRADLE training package consisting of short animated film, interactive sessions, booklet and posters. There were two sets of training materials available, one for facility HCP and one for community HCP with very limited resources or no formal training.

The CRADLE package content covered:

- How to use the CRADLE VSA.

- Maintenance of the CRADLE VSA.
- Basic overview of clinical assessment and management of pre-eclampsia/eclampsia and shock in relation to the traffic light alerts.

The local implementation team and research team delivered one-off interactive group training sessions lasting 2-4 hours to local stakeholders and representative HCP from each of the clinical areas in the cluster. This included a presentation on the background of the CRADLE VSA and the importance of measuring vital signs in pregnancy. This was followed by a demonstration of the features and use of the CRADLE VSA and small group practice using the CRADLE VSA. Training finished with interactive clinical scenarios exploring the use of the CRADLE VSA with available guidance and resources. Attendees were given training materials and CRADLE VSA devices to disseminate to their clinical areas. The implementation team attended each clinical area over the subsequent days (depending on cluster size) to support dissemination and hold interactive sessions.

The core components of the intervention (provision of the CRADLE VSA devices, animated films, posters and content of the training presentation) were standardized across all sites. The way the core components were delivered was adapted to meet the needs of the site. This intervention can be described as complex (Craig et al., 2008) because it comprises multiple interacting components that require considerable shift in the behavior of recipients. It is also being implemented at multiple levels of low-resource health services and will affect multiple outcome measures.(Craig et al., 2008) In the main trial, the intervention will be compared to routine maternity care with clinical assessment and management according to local guidelines. Vital signs measurement is normally undertaken with a variety of BP devices where these are available, which are rarely validated in pregnancy.

Study Design

For this feasibility study, the 10 clusters involved in the main trial collected the primary outcome as defined at that time: a composite of maternal mortality or major morbidity (one of maternal death, ICU admission (or predefined equivalent), eclampsia, stroke, or hysterectomy, with no double counting). Data were collected from existing healthcare facility registers, maternity records, maternal mortality reports and HCP at the discretion of the local research team. Anonymised data were recorded onto a paper form and transferred by the research team onto a purpose-built online database (MedSciNet).

The components of the mixed methodology assessment of the acceptability and feasibility of the CRADLE programme components, undertaken in the three non-trial sites are shown in Table 8.

Table 8 Outcomes, method of measurement and time of measurement in the CRADLE-3 feasibility study.

Outcome		**Method of Measurement**	**Time of measurement**
Feasibility	Fidelity	Duration of training	At training
	Dose	Proportion of staff trained	At training
		Number of facilities included	At training
	Adaptations to fit context	Observation of training	At training
	Understanding of training materials	Questionnaires (n=30 each site)	Post training
		Action Log of Clinical Practice (n=30 each site)	For 1-month post training
Acceptability		Stakeholder Interviews (n=5 each site)	3 months post implementation
		Stakeholder Focus Group (n=1 each site)	3 months post implementation

In order to explore potential mediators of action a purposive sample of HCP were requested to complete action logs of clinical practice to evaluate their referral practice. In these action logs, HCP were requested to record any “yellow” or “red” EWS with the action they took, for example ‘administered anti-hypertensives and referred to hospital today’. This was compared to baseline information of available resources to interpret how HCP had understood and interpreted the training. Questionnaires assessing knowledge of when and how to use the CRADLE VSA and how to interpret the results were filled after training by a random sample of participants.

We undertook semi-structured interviews and focus groups (guides available on request) 4-10 weeks after implementation. This time was selected to allow sufficient experience of the VSA in clinical practice whilst allowing time to make improvements to the intervention within the funding timeline. The aim of these was to further knowledge on the acceptability of the device features gained from a previous observational study of the CRADLE VSA (CRADLE-2)(Hannah L Nathan, 2018) by exploring the feasibility of implementing the CRADLE package and how incorporating it into routine care might change behaviour. Participants were selected through purposive sampling to ensure representation of different HCP cadres in hospital and community care. Participants were approached face-to-face and gave written informed consent to participate in the qualitative study. The interviews were recorded and transcribed verbatim for further analysis and field notes were recorded. Content and notes were reviewed iteratively to identify further participants until data saturation was achieved. Two data coders that were independent to the interviewers undertook analysis using QSR NVivo 11 software.(QRS, Vic, Australia) We used the framework method with a coding framework that draws upon the study objectives, logic model and interview guide.(Ritchie J, 2003., Gale et al., 2013) New concepts initiated by participants that could not be categorized within the initial scheme were coded using an inductive approach and added to the framework. The

COnsolidated criteria for REporting Qualitative research (COREQ) Checklist was used to report the methodology and findings.(Tong et al., 2007)

2.4 Results

Development of Trial Tools

We developed the training materials and data collection tools based on the experiences of the previous CRADLE projects.(de Greeff et al., 2008, El Ayadi et al., 2016, Nathan et al., 2015b, Nathan et al., 2015a, Nathan et al., 2015c) It was necessary to create a training package that could be disseminated quickly in multiple contexts and easily understood by every cadre of HCP with different resources available. Therefore, we selected animated film as the main component so that voice overs could be translated at minimal additional cost and it could be disseminated widely onto smart phones by Bluetooth. Feedback from end-users, health service managers and implementation experts were incorporated.

We created a logic model to depict the components of the intervention, how they may interact to produce change and what the anticipated outcome of that change may be (Figure 22).(W.K. Kellogg Foundation, 2004, Kirby, 2004) This was developed based on the evidence described in the introduction with input of the research team and key stakeholders. These included representative HCP and service managers from our LIC trial sites and implementation experts. The moderating factors and anticipated changes to practice in the logic model were utilized to inform the process evaluation outcome measures.

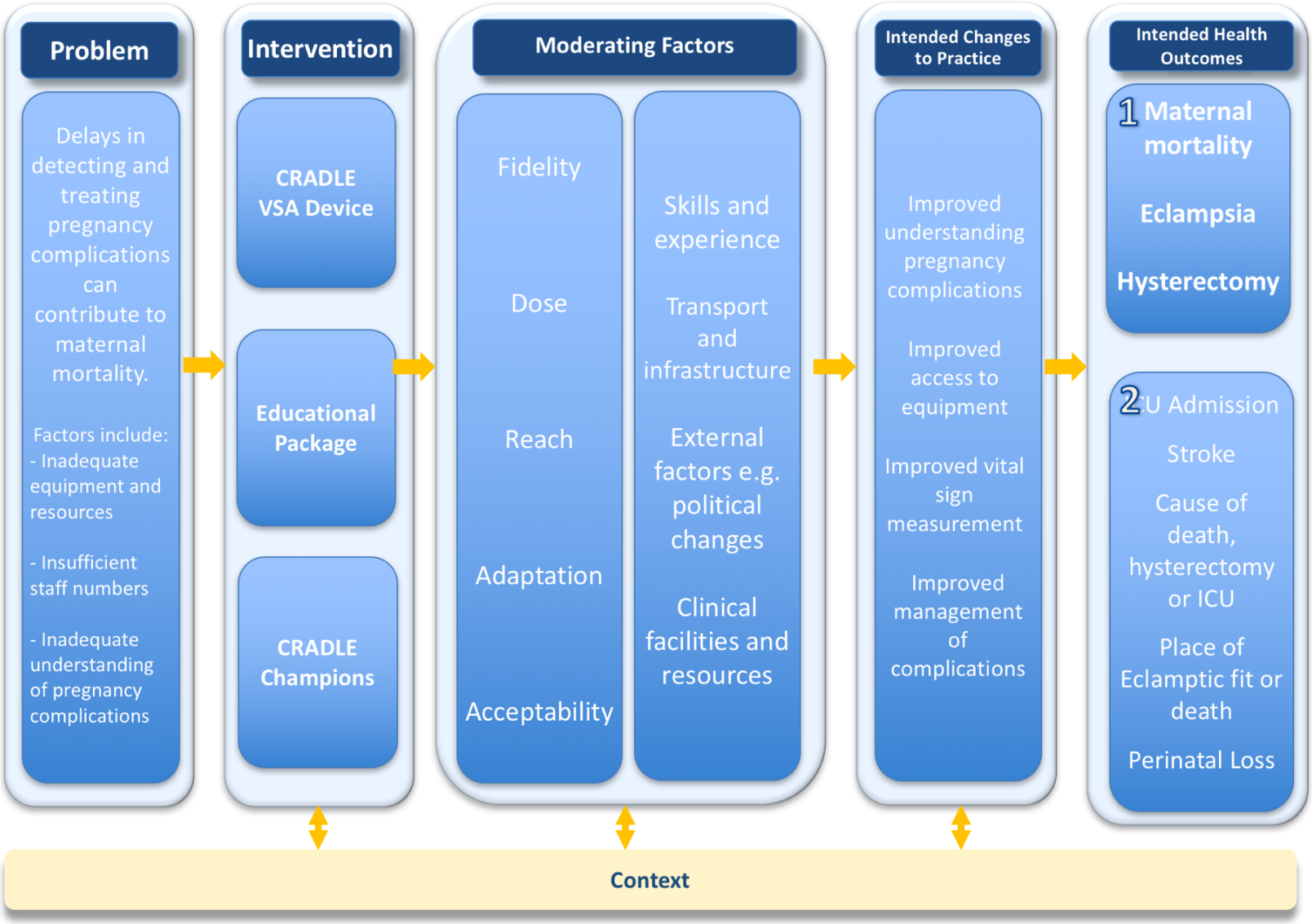


Figure 22 Logic model for the CRADLE-3 intervention

Feasibility of Implementation

The intervention was implemented in three regional hospitals, one from each site, together with 61 associated primary healthcare facilities. The proportion of staff trained, and the duration of training is shown in Table 9. In India and Ethiopia, we translated the training materials and in India the graphics of the poster and booklets were altered to be more culturally appropriate. In all countries the guidance for management of pre-eclampsia, haemorrhage and shock, which was based on WHO guidelines,(World Health Organisation, 2011, World Health Organisation, 2012b) was adapted to incorporate locally available resources and infrastructure.

Table 9 Fidelity and dose of implementation

Study Site	**Number of primary health care facilities involved**	**Proportion of HCP trained**	**Duration of training**	**Devices Distributed**
Masvingo, Zimbabwe	21	90% (n=92)	8 days	62
Bishoftu, Ethiopia	3	85% (n=37)	3 days	29
Ramadurg, India	37	95% (n=75)	2 days	53

In total, 108 questionnaires were distributed and 97 fully completed by HCP and analysed, 16% by HCP working in primary level facilities and 84% in secondary level facilities. This represents 48% of those trained. Of these, five were doctors, 78 were nurses and midwives and 15 were allied HCP. The majority of respondents had more than five years of service (1-5 years n=28, 29%; 6-10 years n=35, 36%; >10 years n=34, 35%). Results indicated a good understanding use of the VSA and interpretation of results with 73 participants (75%) scoring more than 75% correct answers. HCP working in secondary care scored higher in questions on how to act in response to abnormal vital

signs than HCP working in primary care (74% (n=60) scoring over 75% correct compared to 56% (n=9) of clinic participants.

Action logs were distributed to 90 HCP and completed by 68 (76%). The level of detail completed was diverse with many participants failing to complete details on medication given or the time frame taken for action. This was reported to be due to the additional burden of work required to complete these logs and this is explored further in the discussion. Analysis of these records was therefore challenging, and results should be interpreted with caution. It was possible to determine that in total, 62 red lights were recorded, indicating severely abnormal vital signs. The majority (n=50, 81%) had optimal care appropriate for the available resources. Of the 12 that did not, five were referred to hospital but within a longer timeframe and seven were reported to look well so no further action was taken.

The action logs demonstrated varying practice in response to a yellow light with a downward pointing arrow. This result indicates a relative low BP compared to the HR. In Ramadurg, India, the majority of these patients were referred to higher level care, compared to fewer in Bishoftu, Ethiopia. This variance highlighted ambiguity in the training materials. This was explored widely with stakeholders and changes made to the training materials accordingly. A yellow down light may be caused by multiple clinical causes of varying importance (such as maternal anaemia which can be common in pregnancy) and therefore greater emphasis was made on assessment of the patient's clinical condition in the final training materials.

Acceptability of the Intervention and Implementation Strategies

A total of 18 interviews and two focus group were undertaken across the three sites in January and February 2016. Participants were approached face to face and provided written informed consent. The participants had limited prior relationship with the

researchers from training and outreach support visits. Individual interviews were undertaken with nine nurses, five midwives, one maternity manager, two health assistants and one doctor. The median age of participants was 25-34 years (n=12) (18-24, n=1; 34-44, n=3; 45-54, n-2), the most common number of years of service was 1-5 (n=8) (6-10 years, n=5; 11-15 years, n=2; >15, n=3). Findings are presented under themes below. Interviews and focus groups were undertaken in private, quiet locations near the participant's place of work with no non-participant observers to ensure confidentiality and allow for an open discussion. Sessions lasted between 15-75 minutes and were undertaken, translated and transcribed by experienced local research coordinators (clinical background) following training from the trial coordinator and senior social scientist (JS).

Use of CRADLE VSA in clinical decision making

It was widely reported that the CRADLE VSA package improved capacity to make decisions about which women require treatment and referral. This was true for HCP in the community who initiated referral as well as those working in facilities who initiated treatment or escalated care to senior staff. The suggested reasons for this were varied. HCP who were previously using auscultatory BP devices reported lack of confidence in accurately auscultating the Korotkoff sounds and therefore reported regularly rounding the BP to the nearest ten or delaying taking action. This was alleviated by the digital display of systolic and diastolic BP and pulse on the CRADLE VSA.

"There, if we get high BP, we used to think and get the BP checked by others, as we had less confidence in that machine. We used to ask others saying that it has shown high BP in our machine and we want to check by you also. Here with this device (CRADLE VSA) we can take decision immediately." Staff Nurse, Hospital, India

HCP also reported that the EWS alerted them to abnormalities in the results which may otherwise not be recognised. This was reported to be mainly because in pressured environments with fatigued staff abnormal results may be missed whereas a red light is an instantly recognisable alarm. This, in combination with the training materials was felt to provide valuable guidance in the action required to manage abnormalities. The majority of HCP reported that this has improved the time taken to recognise pregnancy complications and initiate treatment or referral. These views are illustrated in the quote below:

"*Yes, more interventions are done and done in a more prompt manner because of the indicators which one can easily refer to and take action promptly. Interventions are done early or immediately because of the indicators that alert the clinicians. They are forced to act quickly even if they refer, but they will have taken some action" Staff Nurse Masvingo, Zimbabwe*

Whilst the majority of HCP felt that the results are accurate and the lights beneficial, there were two HCP who reported that they did not always act on the lights because they were confused. They felt that the yellow light was reported too frequently when patients appeared well. The quote below demonstrates this:

"But what we are observing is that for majority of women it is showing yellow with down arrow. But the patient is stable, normal, she is not sick and she is well. In such situations we feel "why it so? The woman is normal, but still why it is showing yellow down"?" Staff nurse, PHC, India.

Other HCP acknowledged that this was a common result but demonstrated understanding of potential causes and how to manage this result. This finding triangulates the results of the Action Log and is explored further in the discussion.

Aid of the CRADLE VSA in escalating care and referral

Nursing HCP reported that when they were previously using auscultatory devices they reported doubt or being challenged when referring cases to medical staff. The improved confidence in the vital signs measurement and the understanding conveyed by the training package was beneficial in escalating care to senior staff. This was also true in convincing women and their families of the need for further monitoring or referral.

"It is helpful in providing immediate care to the patient. As everything is given there (booklets and poster) like the patient has to be referred within 4 hours or within 1 week...etc., we call the attenders and convince them, to refer the patient at the earliest." Staff Nurse, Gokak, India

The majority of HCP reported an increase in the number of vital sign abnormalities detected; however, the reported impact on the rate of referrals varied between countries. All participants from India reported an increase in the number of referrals. The number of hypertensive patients referred was increased as mild hypertension was considered more seriously. The number of patients with low BP detected and referred was also noted to increase. In Zimbabwe and Ethiopia responses were mixed with some reporting a reduction in referrals due to improved understanding of vital signs and confidence in initiating treatment peripherally. A quote to illustrate this is:

"because of the indicators the referrals have decreased, now we know when to refer and we now don't refer all patients for the sake of referring." Nurse, Clinic, Zimbabwe

Use of results to finalise implementation strategies

The MRC Guidance and supporting documents highlight that the pilot data should be used to shape the intervention and implementation strategies. Following the completion

of this feasibility study, the experiences of implementation and input from a stakeholder meeting across all sites in February 2016 were used to agree a number of changes prior to the main trial. The choice of implementation strategy was guided by the Expert Recommendations for Implementing Change project (Powell et al., 2015) with the aim of improving understanding of the training materials and overcoming identified barriers to use. Table 10 presents the key issues experienced through the feasibility study alongside quotes to support this and the implementation strategies or changes we have selected.

Table 10 Barriers to measuring the vital signs and using the VSA and actions made prior to the main trial

Issue from Feasibility study	**Supporting quotes from Interviews and Focus Group**	**Changes required after feasibility study**
Understanding of yellow light with down arrow	*"When the pregnant woman comes to us she is well and it shows yellow down (laughs); in that case how to interpret?" Staff Nurse, India*	Training materials updated to explain the reason for each colour light and guidance updated to place greater emphasis on how to assess the woman to decide *if* further action or referral is required.
Problems with charging the VSA	*"… some workers say that the battery life is good but I have to charge it for daily. If I have to go for BP check-up today I have to charge it first." Staff Nurse, India*	- Interactive training session developed which incorporates guidance on charging and accountability for charging. - Including explanation that more than 100 readings can be taken even when the battery low sign is showing and overcharging will damage the battery.
Provision of Charger	*"the package should include the charger rather than USB cable only so that we can charge it easily" Staff Nurse, Zimbabwe*	Chargers provided in addition to the cable that comes as standard in the package.
High staff turnover / incapacity to train all staff at once	*"Initially, we faced difficulty. There were nurses using it during the night shift and they were not trained." Staff Nurse, Bishoftu*	Designated CRADLE Champions in each facility identified to provide ongoing local training and support for CRADLE VSA
Unsupportive seniors	*"Recently during an ANC clinic, he enquired which device we are using; we said, "we are using the CRADLE device…" then he said "oh… it shows yellow down to all pregnant women, so better do not use it"." SN, India*	- Designated CRADLE Champions identified to provide ongoing local training and support for CRADLE VSA - Engage Local Opinion leaders prior to implementation
Need for equipment	*"…no BP machines at all, the one we had was no longer working." Staff Nurse, Zimbabwe*	Ensure adequate supply of VSA available

A key implementation strategy that we selected as a result of the feasibility findings was the identification and training of CRADLE champions. These are clinical staff and local leaders who receive more in-depth training about the device and are equipped with the tools to support the use of the VSA in their area. Whilst we wanted the trial to remain pragmatic and replicable, this strategy was chosen to support ongoing local training and build local capacity for maintenance. The importance of the support of the implementation team on the effectiveness of the intervention was also noted during the study and added to the logic model as a core component of the intervention. In order to maintain the pragmatic trial design, it was decided not to quantify this support but for the research team to observe it during the routine monthly site monitoring and be aware of its potential impact.

Main Trial Primary Outcomes

As the main trial has a stepped wedge design with an intervention incorporated into routine care, cluster level consent instead of individual was appropriate. This was agreed as preferable by all sites during the development work. All ten trial sites gained ethical and local approval for participation in the main trial. Nine of them achieved this before or during the feasibility phase and were therefore able to commence data collection, with six sites completing a full three months of data collection. During this formative phase a total of 844 outcome events (any one of eclampsia, maternal death, hysterectomy, ICU admission or stroke) occurred in 681 women from nine of the ten sites. On average, the number of women experiencing events each month varied from five in Gokak, India to 63 in Zomba and South-Eastern Malawi (median 19.6, standard deviation 19.6). The most common outcome was eclampsia (n=386, 46%) followed by ICU admission (n=271, 32%), hysterectomy and maternal death (n=96, 11%; n=91, 11% respectively) and stroke (n=2, 0.2%). The tools for data collection were found to be appropriate. Methods of data collection were discussed and optimised based on the existing resources available in each site. Outcomes were triangulated across multiple sources (including referral

registers, ward registers, patient records, local mortality and morbidity records, active case finding) to ensure data completeness and all outcomes checked to avoid double counting.

These outcomes had been intended as unequivocal markers of severe maternal mortality and morbidity. However, during the process of data collection it became apparent that ICU admission was dependent on availability of services, which varied greatly between clusters and therefore this was not a reliable proxy marker of maternal morbidity. The number of strokes reported across all sites was just two, both from one site. It was therefore prospectively decided that for the main trial the composite primary outcome would include only eclampsia, maternal death and emergency hysterectomy. Given that the size of clusters varies greatly, it was agreed that the number of deliveries would be counted as a surrogate denominator so that results for the main trial could be presented as an event rate per 10,000 deliveries. These prospective amendments were added to the trial registry (ISRCTN41244132).

Randomisation and Power Calculation

An estimated event rate from the data was used to inform the randomisation sequence and power calculation of the main trial. With so few centres to be randomised there was a risk of unbalance – for example that by chance the centres with the highest event rates might be allocated to the intervention at the end of the study, giving a false impression of a low event rate in centres which received the intervention early, and hence a biased estimate of the treatment effect. Although the planned analysis would correct for this, to further minimize the problem, a restricted form of randomisation was used, so that the rank correlation between the initial event rate, and the order of randomisation was zero. For logistic reasons, the two centres outside Africa: Cap Haitien (Haiti) and Gokak (India) were treated as one centre for randomisation (but not for analysis).

First the overall rate of the primary outcome was determined in the nine clusters and each cluster given a corresponding rank r from one to nine (e.g. the cluster with the lowest event rate given rank 1 up to the highest event rate given rank 9). Then a provisional list of the order of intervention was determined for each cluster using computer-generated random numbers based on an arbitrary random number seed. Spearman's rank correlation rho between r and l was determined. If the rank correlation was not equal to 0, the list was discarded, and the process repeated until an acceptable order was determined. The first acceptable randomly-generated list was retained. This resulted in a near-zero Pearson's product-moment correlation of -0.019 between the event rate and the order of randomisation.

Based on these data, our sample size estimation was carried out by the trial statistician, using Stata version 13.1 and the methods of Hemming and Girling (Hemming K, 2014a). For the purpose of the power calculation, an assumption that there are at least 4000 deliveries per cluster per month was made (or 8000 per cluster period of two months) and at least nine clusters, each observed for 20 months (ten time periods of two months each). Our feasibility data indicated a baseline event rate of 1% and we have anticipated a 25% reduction in this to 0.75% post intervention. We would require a total of 2450 outcome events with a coefficient of variation of 0.4 and an ICC of 0.0085, to have power of 95%.

2.5 Discussion

This paper aims to describe the mixed methodology feasibility study exploring the acceptability and feasibility of introducing the CRADLE package into routine maternity care in LMIC along with the feasibility of the main trial data collection processes. The key findings are that the intervention can be delivered with high fidelity and dose and incorporated into routine maternity care successfully in different contexts without major

adaptation. In addition, we have confirmed that the methods of collecting the main outcome data are feasible and can be maintained for consistency and this data has successfully been used to improve the study design, randomisation and power calculation.

The MRC framework stresses the importance of quality development work to avoid problems with acceptability, compliance, recruitment and retention. Yet methodological research suggests that pilot studies are often poorly performed and few are published.(Eldridge et al., 2004) Most published examples of complex interventions demonstrate valuable learning from pilots; for example, the exploratory RCT of an intervention to reduce alcohol related harm demonstrated that whilst the trial was methodologically feasible, poor enthusiasm resulted in low fidelity thus the conclusion that the intervention would need to be enforced in future work.(Moore et al., 2012) However, published description of its use in the field of maternity and in LMIC is scarce.

Through this feasibility study we have experienced the practicalities of undertaking a pragmatic process evaluation in a low-resource setting. The MRC supporting guidance provides explanation for each of the key dimensions of implementation that could be measured and guides researchers to select the most important questions to investigate. Whilst this is a strength of the framework, as it ensures comprehensive evaluation of implementation, it provides little guidance on how to select suitable outcome measures for each dimension. This is especially challenging when working in a resource-poor environment with the additional burden of high workload and limited or heterogeneous routine data recorded compared to high resource environments. In this feasibility study, measuring multiple components compared to baseline was not possible within the short time frame. The proportion of people trained centrally, and time taken for training were selected as simple surrogates of fidelity and dose. However, in the qualitative work the majority of HCP reported the VSA was easy to use and it was possible to commence use

just on reading the training materials so the extent that these measures may impact the effectiveness of the program is unknown. In the main trial the number of core components delivered in training and how they were adapted to context were added to the measure of fidelity.

The MRC Guidance advises using the logic model to identify causal assumptions and guide selection of research questions. In the CRADLE Logic model, the assumed changes to practice include improving access to equipment. Therefore, in the trial we will capture the proportion of HCP that have access to a working BP machine before and after implementation. A further assumed change is improving vital sign measurement and management of complications. In this feasibility study, the action log of referral practice was poorly received and completed due to the extra burden of work it demanded. For the main trial, we chose to explore change in practice during the qualitative work rather than during structured observation due to the large variety of normal practice in different countries. The qualitative work also highlighted that number of women referred to higher level care was a potential key moderator. Therefore, after stakeholder discussion across our sites we agreed to measure the proportion of women presenting for maternity care that had their BP measured and the proportion that were referred to higher level care. Due to the intensity of this data collection it was agreed this would be measured for a period of four weeks before implementation and four weeks, three months after the device was introduced to allow time for familiarization of the VSA in routine maternity care. We found the process of identifying potential factors that may impact on the success of the trial and tailoring outcome measures accordingly was achievable for a team of predominantly newcomers to the field of implementation. It was also beneficial in assuring that assumptions are shared between stakeholders.

Strengths and Limitations of the study

We describe the feasibility testing of the CRADLE intervention prior to a fully powered trial. This was guided by the MRC guidance and was undertaken over a 6-month period; results are therefore applicable to others working in restricted funding periods. Feasibility and pilot research are often skipped or inadequate to fully inform the main trial and rarely published to inform others researching similar areas. In a situation where a complete development phase is not possible due to the stepped wedge design we demonstrated that our event rate in the main trial sites is sufficient to have adequate power. We undertook formal qualitative analysis to explore the acceptability of the program components and feasibility of implementation. We did not assess knowledge of vital signs measurement prior to training and therefore results should be interpreted with caution.

Conclusions

This feasibility study demonstrates that the components of the intervention were acceptable and the methods of implementing successful. Qualitative work identified key moderators that have informed the main trial process evaluation. Changes to the training package, implementation strategy, study design and processes were identified to optimise the main trial implementation. Carrying out these changes in practice, (for example to the data collection forms, database and graphics of the training materials) were challenging within the six-month allocated time frame of this feasibility study. If larger changes had been required, for example to the components of the intervention which would require re-testing, this would not have been possible. Funders recommending that a development phase is incorporated into a standard 3-year funding period might therefore take into consideration the time taken to undertake the work, analyse results and incorporate changes into the study to ensuring meaningful improvements can be made.

Concurrently assessing the feasibility of the trial outcomes in the 10 main trial sites and the implementation processes in geographically distant sites was necessary to avoid contamination of the trial area. Whilst undertaking this in multiple sites required additional work, it allowed for greater understanding of how the intervention could be adapted in each context and how the main trial will run. The MRC Guidance and supporting documents provided a valuable tool to guide the overall design of this study and the development of the process evaluation for the main trial. This study presents a real world worked example that has utilised this guidance to refine the intervention, main trial outcomes and process measures.

3 Effect of a novel vital sign device on maternal mortality and morbidity in low-resource settings: a pragmatic stepped wedge cluster randomised-controlled trial

3.1 Abstract

Background:

In 2015, over 800 women died in pregnancy and childbirth every day. Obstetric haemorrhage, sepsis and HDP account for over 50% of maternal deaths worldwide. There are effective treatments for these pregnancy complications, but they require early detection by measurement of vital signs and timely administration to save lives. The CRADLE VSA accurately measures BP and pulse and calculates SI. Results are displayed on a traffic light EWS.

Methods:

We conducted a pragmatic, stepped-wedge randomised-controlled trial in ten clusters across Africa, India and Haiti, introducing the device into routine maternity care (ISRCTN 41244132). Each cluster contained at least one secondary or tertiary hospital and their main referral facilities. The primary composite outcome was at least one of eclampsia, emergency hysterectomy and maternal death per 10,000 deliveries.

Results:

Between April 1st 2016 and November 30th 201, among 536,223 deliveries, the primary outcome occurred in 4067 women, with 998 maternal deaths, 2692 eclampsia cases, 681 hysterectomies. There was an 8% decrease in the primary outcome from 79·4/10,000 deliveries pre-intervention to 72·8/10,000 post-intervention (odds ratio (OR) 0·92, 95% CI 0·86–0·97; p=0·006). After planned adjustments for variation in event rates between and within clusters over time, the unexpected degree of variability meant we were unable to judge the benefit or harms of the intervention (OR 1·22, 95% CI 0·73–

2·06; p=0·45). There was a significant reduction in the rate of emergency hysterectomy (OR 0·21, 95% CI 0·07-0·66; p=0·007) but not eclampsia (OR 1·91, 95% CI 0·91-4·03; p=0·09), or maternal death (OR 0·79, 95% CI 0·30-2·09; p=0·65). There were significant differences between individual clusters.

Conclusions:

There was an absolute 8% reduction in primary outcome during the trial, with no change in resources or staffing, but this could not be directly attributed to the intervention due to variability. Stepped-wedge trials across multiple countries have methodological challenges.

3.2 Background

Maternal mortality remains a challenge worldwide, especially in low-resource settings where in 2015, an estimated 303,000 women died from complications of pregnancy and childbirth.(World Health Organisation, 2015b) The leading direct causes of maternal mortality are obstetric haemorrhage (27·1%), hypertensive disorders (14·0%), sepsis (10·7%) and abortion complications (7·9%).(Say et al., 2014) There are simple, evidence-based interventions available for the majority of these conditions.(Campbell and Graham, 2006) However, in low-resource settings, delays in presenting to care, reaching care and receiving this care all contribute to high maternal mortality.(Thaddeus and Maine, 1994)

Vital sign measurement is the first step in recognising women at risk of deterioration, (particularly from hypertension, obstetric haemorrhage and sepsis) and therefore in initiating treatments that can prevent potentially catastrophic maternal and perinatal complications.(World Health Organisation, 2005a) EWS allow for tracking of vital signs to alert HCP to abnormalities and allow earlier action. They are widely used in HIC.(Isaacs et al., 2014) Several studies have found EWS to be beneficial at predicting

maternal morbidity and mortality but these are generally small, retrospective studies.(Singh et al., 2012, Ryan et al., 2017, Hedriana et al., 2016, Carle et al., 2013, Paternina-Caicedo et al., 2017, Lappen et al., 2010, Edwards et al., 2015) Only one prospective, non-randomised study has demonstrated that implementing a paper-based EWS across six high-income pilot hospitals resulted in a significant reduction in a composite of maternal morbidity compared to non-pilot sites.(Shields et al., 2016) However, to be effective EWS require accurate measurement and documentation of vital signs followed by calculation of risk and appropriate escalation or action. In low resource settings, inadequate access to reliable equipment(Baker et al., 2012, Betrán et al., 2018), overstretched staff(World Health Organisation, 2006) and poor understanding of pregnancy complications and vital signs monitoring(Boene et al., 2016) can potentially lead to delay in identifying and initiating treatment in those most at risk.

The CRADLE VSA is a semi-automated device that measures BP and HR and calculates SI. It has been extensively tested and is validated as accurate in pregnant women, including those with high and low BP.(de Greeff et al., 2008, Nathan et al., 2015b, Nathan et al., 2015a) Qualitative implementation evaluation in low-resource settings has determined that it is easy to use, robust and suitable for use by any cadre of HCP, even those without extensive training such as CHWs.(Nathan et al., 2018a) Results are displayed digitally and on a traffic light EWS which indicates abnormal vital signs (Figure 23).(Nathan et al., 2018a) This is important in low-resource settings where routine clinical tasks, such as vital signs measurement, are often undertaken by those with minimal training and CHWs also play a vital role in maternity care, often being the first point of contact and an essential link to clinical services.(Campbell and Graham, 2006, Schneider et al., 2016)

Hypertension Thresholds	Blood Pressure (mmHg)
Red light & Up Arrow	≥ 160 and / or≥ 110
Yellow Light & Up Arrow	140 – 159 and / or 90 – 109
Green Light	< 140 and < 90
Shock Index Thresholds	**Shock Index (HR / sBP)**
Red Light & Down Arrow	≥ 1.7
Yellow Light & Down Arrow	0.9 – 1.7
Green Light	< 0.9

Figure 23 Thresholds that trigger the traffic light early warning system on the CRADLE VSA

The primary aim of the trial was to determine whether implementation of the CRADLE VSA and an education package into community and facility maternity care could reduce a composite of all-cause maternal mortality or major morbidity (eclampsia and hysterectomy).(Nathan et al., 2018b) This trial was preceded by a six-month feasibility study to develop and improve the intervention and implementation strategies,(Vousden et al., 2018) informed by guidance from the MRC for evaluation of complex interventions.(Moore et al., 2015)

Research in Context

Evidence before this study

We searched PubMed for original articles published in English prior to July 1, 2018 with the search terms “maternal OR maternity OR pregnancy AND early warning”. This identified eight studies (seven undertaken in HIC), which examine the predictive capacity of EWS in pregnancy. No clinical trials or systematic reviews were identified. Despite this, it is widely recognised that delays in recognising and initiating treatment for pregnancy complications contributes to maternal mortality. Therefore, EWS are consistently recommended in HIC. In low-resource settings inadequate access to accurate vital signs equipment and trained staff further adds to delays in detecting pregnancy complications. To our knowledge, no study has yet investigated novel solutions that integrate EWS into accurate equipment to reduce maternal morbidity and mortality in low-resource settings.

Added value of this study

This stepped wedge randomised controlled trial provides the first evaluation of a novel EWS and accurate vital signs device in preventing maternal morbidity and mortality in low resource settings. In ten clusters in eight LMIC, introduction of the device with an educational package into routine maternity care reduced a composite of maternal morbidity and mortality, but the variation in event rates between and within clusters over time, meant this reduction could not be attributed to the intervention, despite over 4000 primary outcome events (maternal death, eclampsia or hysterectomy) amongst a population of over half a million maternities. Very few trials of a similar size have been undertaken in maternity populations, and to our knowledge, none has evaluated an EWS.

Implications of all the available evidence

The existing evidence has shown that EWS may be beneficial in detecting pregnancy complications earlier in HIC. This trial has demonstrated a reduction in maternal morbidity and mortality during the trial period, with no change in resources or staffing. However, the unexpected degree of variability within clusters over time and between clusters meant that this reduction cannot be attributed to the intervention. Evaluation of the intervention in individual countries may elucidate mechanisms by which it impacts on outcomes. To our knowledge this is the first stepped wedge RCT undertaken across multiple countries and continents; the design was chosen after careful consideration, including the intention to leave all ten sites equipped with vital sign monitoring devices. We encountered unanticipated methodological challenges which provide valuable learning for future research and inform the trial design of future international stepped wedge trials.

3.3 Methods

Design and Study Setting

This pragmatic, mixed-methods SW-CRT evaluated the CRADLE intervention in routine maternity care in low-resource settings. All methods were pre-defined, published and registered with ISRCTN (41244132) with no important methodological changes. Ten clusters across eight countries were identified and agreed to participate. These were in Addis Ababa in Ethiopia, Cap Haitien in Haiti, Freetown in Sierra Leone, Harare in Zimbabwe, Gokak in India, Kampala and Mbale in Uganda and Lusaka and Ndola in Zambia. Each cluster comprised at least one urban or peri-urban secondary or tertiary health facility providing comprehensive emergency obstetric care with multiple peripheral facilities that referred to the central hospital (Nathan et al., 2018b). Facilities were identified by the local primary investigators as the main facilities that refer to the central hospital within a feasible geographical area. Community HCP were included in implementation in clusters where they were supported at a district level and active in routine maternity care provision (Ndola and Cap Haitien). Clusters crossed over from control to the CRADLE intervention in one of nine steps at 2-monthly intervals with CRADLE devices replacing existing equipment at the randomised time-point.

Population

All HCP working in the cluster facilities had access to the intervention. All women identified as pregnant or within the 6-week postpartum period, presenting for maternity care in a cluster facility or to community HCP, were exposed to the intervention. There were no exclusion criteria.

Intervention

Prior to the intervention, routine maternity care utilised a variety of medical devices (where previously available) with management by local guidelines. The CRADLE VSA

and training package was iteratively developed and piloted as previously described (Nathan et al., 2018b). At the randomly allocated time-point, the training package was delivered in interactive group sessions to HCP from each of the clinical areas in the cluster facilities. Some HCP in each cluster became CRADLE Champions and provided ongoing training and support in their clinical areas. The local implementation team provided regular support to all facilities with at least monthly contact. Existing equipment for measuring vital signs was usually removed from clinical use unless there were specific functions needed (repeated automated measures in a high dependency unit). We did not include a transition period; outcomes occurring after implementation start were allocated to the intervention group.

Outcomes

The primary outcome was a rate of a composite of maternal mortality or major morbidity: at least one of maternal death (all-cause mortality), eclampsia (occurrence of generalised convulsions with increased BP in absence of epilepsy or another condition predisposing to convulsions) or emergency hysterectomy (surgical removal of all or part of the uterus) per 10,000 deliveries per month, occurring during pregnancy, labour or within 42 days of delivery. Pre-defined secondary maternal outcomes were the individual components of the primary outcome (eclampsia, emergency hysterectomy and maternal death), ICU admission, defined as admission or referral to a specific ICU or equivalent defined highest-level care environment and stroke. Secondary perinatal outcomes, collected per 1000 woman with a primary outcome, were the rate of stillbirths and neonatal deaths. This was defined as death within 28 days of delivery after 28 weeks' gestation.

Each cluster included primary (first point of access), secondary (first referral point) and tertiary facilities (specialty referral facility). Maternity unit staffing levels (Doctors, nurses, midwives, clinical officers and community HCP in Ndola and Cap Haitien where active in routine care) and availability of key resources (magnesium sulfate, ICU beds and

capacity for blood transfusion) were recorded throughout the trial period. Major changes to infrastructure, patient payment requirements or environmental conditions were evaluated each month. Service impact was assessed by the proportion of women referred from peripheral facilities to higher-level care (collected for a four-week period prior to and three months after implementation). There were no changes to pre-specified outcomes during recruitment and only pre-specified analyses were undertaken.

Data Collection

Prior to the trial start, data collection methods were optimised based on existing resources available in each site. Outcomes were triangulated across multiple sources (including referral registers, ward registers, patient records, local mortality and morbidity records and active case finding) to ensure data completeness. Source data consistency and quality were monitored by the research team with a proportion verified by the UK team. There were no formal stopping rules. As the intervention itself was not considered likely to lead to adverse events, and all major adverse pregnancy complications were included as outcomes, no additional adverse event reporting was undertaken. The trial ended after 20 months as planned.

Randomisation and masking

The unit of randomisation was the cluster. A restricted method of randomisation selected a randomisation order with zero rank correlation between events per month and order of randomisation, to minimize imbalance between intervention and control periods due to anticipated variation in the primary event rate between clusters. The order in which the clusters received the intervention was a computer-generated randomly-allocated sequence performed by the CRADLE statistician (PTS). All clusters were masked to the order until two months prior to receiving the intervention, when the next cluster to receive the intervention was informed. By nature of the intervention, this trial was non-masked.

The two smallest clusters were randomised at the same time. Data were gathered monthly, with 20 time-periods of one month.

Ethics and Consent

Ethical approval was granted by the King's College London Research Ethics Subcommittee at (LRS-14/15-1484) and in all countries prior to the trial start. Institutional-level consent on behalf of the cluster was obtained.(Hemming et al., 2015)

Sample size calculation

Sample size estimation was informed by data from the feasibility phase, and carried out using Hemming and Girling's methods.(Hemming K, 2014a) Assuming 4000 deliveries per cluster per month, with nine clusters, each observed for 20 months, and a baseline event rate of 1% with a reduction to 0.75% post-intervention, a total of 2450 outcome events was required to have power of 95% with a coefficient of variation of 0.4 (judged to be high, but plausible, based on our pilot data) and an ICC calculated as 0.0085 for this study design.

Statistical Analysis

Statistical analyses were undertaken in Stata version 14.2 (by PTS). The planned comparison using risk ratios was undertaken but did not converge for the majority of results. This is a common finding in analyses of rates, therefore results are reported as odds ratios. The main analysis used logistic regression with generalised estimating equations and a population-averaged model.(Hussey, 2007) For the primary analysis of the primary outcome and its individual components,(The European Agency for the Evaluation of Medicinal Products, 2002) we adjusted for three predictors: cluster (categorical), time from start of study (continuous; with an interaction between cluster and time so that each cluster had its own underlying time trend), and total time on the randomised intervention, with time before intervention given as zero (continuous). This

resulted in separate linear time trends in each cluster as pre-specified. The model for intervention analysis allowed for separate linear trends in each cluster before and after the intervention or a change in slope of the line at the time the intervention was introduced (linear splines or “bent stick”). This was an amendment from the planned single linear trend in each cluster with a sudden change (or step) at the time of the intervention, but no change in slope (“trend and step”) as it achieved greater stability; both analyses are presented and were adjusted for the same predictors.

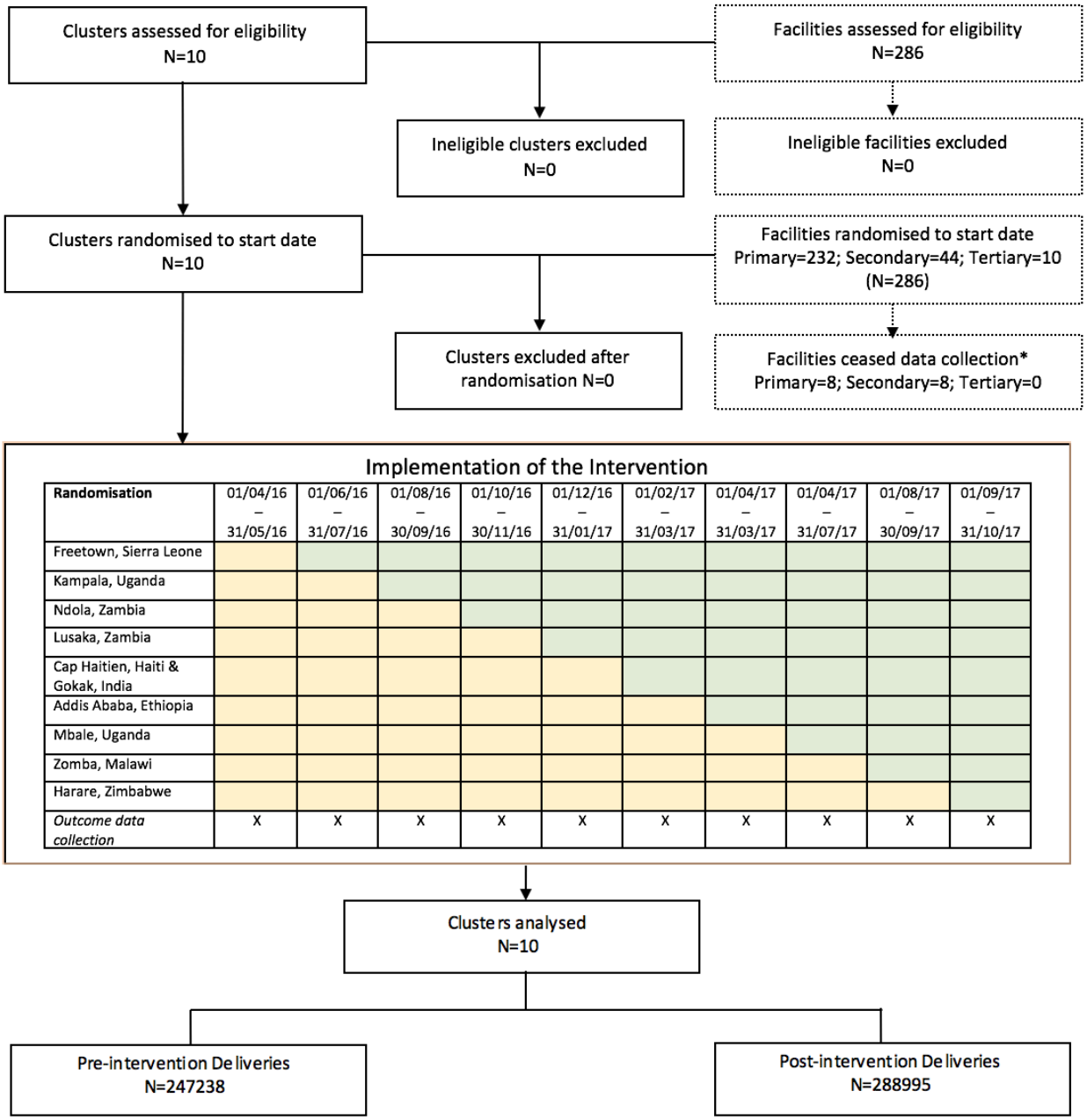
Results for individual clusters were also analysed using fixed linear trend and a step at the start of intervention as predefined because bent-stick models were not reliable for clusters that implemented early or late and therefore had few data points with or without the intervention. As individual patient data were collected only for known cases we have to treat all other women as having no event and therefore have no information on which to estimate the extent of missing data. This is not expected to have changed following the intervention.

Sensitivity analysis removing the week prior to and after implementation was originally intended, but proved impossible, as only monthly delivery data could be collected. Auto-regressive correlation allows for decreasing correlations between observations over greater time periods; sensitivity analysis for alternative correlation structures was undertaken as planned. Confidence Intervals were calculated by generalized estimating equations and robust standard errors adjusted for clustering. We planned to adjust for any significant differences in the characteristics of clusters (number of facilities, obstetric resources and personnel) before and after the intervention, but none were found.

3.4 Results

Trial Sites

We approached and included 10 clusters, including 286 facilities (Figure 24). Clusters were well balanced in both groups with no significant differences in their characteristics, including average deliveries per cluster per month (p=0.49) (Table 11).



*Eight primary and eight secondary facilities stopped providing maternity services or closed during the trial.

Figure 24 Cluster and facility enrolment, randomisation, implementation and analysis

Table 11 Characteristics of all clusters, including month-by-month variation through the course of the study

Characteristic	**Pre-intervention**	**Post-intervention**	**Average throughout trial**	**Rate of change (% per month (95% CI))**	**Difference % (95% CI))**
Total Number of deliveries	247238	288995	NA	NA	NA
Number of deliveries per month: Mean (SD)	2472 (1569)	2890 (2291)	2681 (1970)	3 (-5 to 11) p=0.46	418 (-713 to 1567) p=0.49
Place of Delivery					
Central Referral Facility: N (%)	1434 (63.4%)	1282 (55.0%)	1358 (59.2%)	0.1 (-0.3 to 0.4) p=0.79	-8.4% (-17.6 to 0.8) p=0.11
Peripheral Facility: N (%)	958 (32.8%)	1523 (41.6%)	1241 (37.2%)	0.1 (-0.2 to 0.4) p=0.68	8.7% (-0.4 to 17.9) p=0.09
Home: N (%)	105 (4.8%)	118 (4.7%)	111 (4.8%)	-0.1 (0.3 to 0.1) p=0.28	-0.1% (-2.4 to 2.2) p=0.92
Mode of delivery					
Caesarean section: N (%)	366 (16.8%)	494 (18.1%)	430 (17.4%)	0.3 (-0.1 to 0.6) p=0.19	1.3% (-2.4 to 5.0) p=0.52
Total Number of facilities					
Number of primary level care facilities	232	224	228	-0 (no trend)	-1.0 (-8.0 to 7.0) p=0.85
Number of secondary level care facilities	44	36	40	-0 (no trend)	1.0 (-2.0 to 1.0) p=0.44
Number of tertiary level care facilities	10	10	10	-0 (no trend)	-0 (no trend)

Total Number of facilities (per 1,000 deliveries)					
Number of primary level care facilities: Mean (SD)	13.8 (15.3)	14.3 (15.7)	14.1 (15.5)	0.0 (-0.4 to 0.4) p=0.96	0.4 (-3.9 to 4.7) p=0.85
Number of secondary level care facilities: Mean (SD)	2.8 (5.4)	2.5 (5.5)	2.6 (5.5)	0.0 (-0.1 to 0.1) p=0.97	-0.3 (-1.9 to 1.2) p-0.66
Number of tertiary level care facilities: Mean (SD)	0.8 (1.4)	0.8 (1.2)	0.8 (1.3)	-0.0 (-0.0 to 0.0) p=0.74	0.0 (-0.3 to 0.4) p=0.89
Obstetric resources					
Capacity for blood transfusion (Mean % of facilities (SD))	28.9% (21.7)	21.3% (16.4)	25.1% (19.5)	-0.1 (-0.3 to 0.1) p=0.42	-7.7 (-22.4 to 7.1) p=0.34
Adult Intensive Care Unit beds: Mean (SD)	11.7 (9.1)	10.1 (9.1)	10.9 (9.1)	-0.1 (-0.2 to 0.1) p=0.35	-1.6 (-6.0 to 2.8) p=0.49
$MgSO_4$ available (Mean % of facilities (SD)	76.2% (25.2)	73.1% (23.7)	74.7% (24.5)	0.2 (-0.1 to 0.6) p=0.21	-3.0 (-16.2 to 10.1) p=0.66
Personnel (per 1,000 deliveries)					
Total doctors in maternity units: Mean (SD)	40.0 (33.4)	38.4 (28.7)	39.2 (31.1)	0.0 (-0.3 to 0.4) p=0.86	-1.6 (-13.7 to 10.5) p=0.80
Obstetrician/Gynaecologist: Mean (SD)	8.9 (8.3)	9.3 (7.6)	9.1 (8.0)	0.0 (-0.1 to 0.1) p=0.82	0.4 (-2.4 to 3.3) p=0.78

Clinical Officers: Mean (SD)	30.5 (34.3)	20.8 (23.0)	25.6 (29.6)	-0.0 (-0.2 to 0.1) p=0.61	-9.6 (-26.6 to 7.4) p=0.30
Anaesthetist (doctor): Mean (SD)	10.0 (11.1)	6.9 (9.8)	8.5 (10.5)	0.1 (-0.0 to 0.1) p=0.17	-3.1 (-9.5 to 3.2) p=0.36
Staff member trained as anaesthetist available 24hrs: Mean (SD)	4.0 (3.3)	5.7 (4.7)	4.9 (4.2)	-0.0 (-0.1 to 0.0) p=0.42	1.7 (-1.4 to 4.9) p=0.31
Midwives: Mean (SD)	67.2 (57.4)	53.7 (41.6)	60.4 (50.5)	0.3 (0.03 to 0.6) p=0.06	-13.5 (-48.8 to 21.7) p=0.47
Nurses with midwifery training: Mean (SD)	77.0 (45.9)	104.6 (86.2)	90.8 (70.3)	-0.5 (-1.8 to 0.9) p=0.51	27.6 (-29.7 to 85.0) p=0.37

Primary Outcome

A total of 4067 women had a primary outcome (one or more of maternal death, eclampsia, hysterectomy) from 536,223 deliveries (Table 12). There was an 8% reduction in the primary outcome in the intervention compared to the control period (79.4/10,000 deliveries pre-intervention to 72.8/10,000 post-intervention; OR 0.92, 95% CI 0.86-0.97). However, after pre-specified adjustments (primary analysis) for variation between and within clusters over time, no significant benefit or harm could be attributed to the intervention (OR 1.22; 95% CI 0.73-2.06). The calculated ICC coefficient was 0.61, much higher than the assumed 0.0085. Sensitivity analysis for alternative correlation structures was undertaken as planned with no significant findings. Sensitivity analysis removing four periods of data where there were external changes within the site (strike action affecting staffing levels in three sites and natural disaster in Haiti) had no impact on the results.

Table 12 Primary outcome, Secondary Maternal and Perinatal Outcomes

	Pre-intervention	**Post-intervention**	**Unadjusted Comparison (Step) (Odds Ratio)**	**Planned Adjusted Comparison (Trend & Step) (Odds Ratio)**	**Adjusted Comparison (Bent Stick) (Odds Ratio)**
Composite of maternal mortality and morbidity	N=247238	N=288995			
Composite (one or more of eclampsia, hysterectomy or maternal death): rate/10,000 deliveries n/N	79.4 1963/247238	72.8 2104/288995	0.92 (0.86-0.97) p=0.006	1.13 (0.85-1.51) p=0.40	1.22 (0.73-2.06) p=0.45
Eclampsia: rate/10,000 deliveries n/N	53.1 1314/247238	47.7 1378/288995	0.90 (0.83–0.97) p=0.005	1.30 (0.82-2.05) p=0.27	1.91 (0.91-4.03) p=0.09
Hysterectomy: rate/10,000 deliveries n/N	12.8 316/247238	12.6 365/288995	0.99 (0.85-1.15) p=0.88	0.87 (0.50-1.52) p=0.63	0.21 (0.07-0.66) p=0.007
Maternal Death: rate/10,000 deliveries n/N	18.2 451/247238	18.9 547/288995	1.04 (0.92-1.18) p=0.56	0.85 (0.65-01.10) p=0.22	0.80 (0.30-2.09) p=0.64
Secondary maternal outcomes					
Stroke: rate/10,000 deliveries n/N	0.5 13/247238	0.3 9/288995	-	-	-
Admission to ICU: rate/10,000 deliveries n/N	14.8 365/247238	8.0 232/288995	-	0.60 (0.39-0.91)	0.79 (0.53-1.17)

Secondary perinatal outcomes (per 1000 births in women with a primary outcome)					
Stillbirth: rate/1000 pregnancies n/N (all women with a primary outcome*)	192 343/1782	259 500/1933	-	1.02 (0.61-1.69)	0.95 (0.87-1.04)
Neonatal death: rate/1000 pregnancies n/N (all women with a primary outcome*)	29 52/1782	40 77/1933	-	-	-

*Excludes 17 women with missing delivery information, 45 women who went home after a primary outcome without delivery and were not followed up, and 290 women who were less than 28 weeks pregnant at the time of the primary outcome and delivery data were not collected.

Secondary Maternal Outcomes

Analysis of the individual components of the primary outcome was pre-specified and is presented in Table 12. There was a significant reduction in the rate of emergency hysterectomy in the intervention period compared to the control period, but the eclampsia and maternal death rates did not significantly change (Table 12). Very few women experienced a stroke, with 13 in the control period and 9 in the intervention period (convergence for comparison not achieved). There was no significant change in the number of women admitted to intensive care (Table 13).

Secondary Perinatal Outcomes

In delivery data, available for 3715 women with a primary outcome (including 123 twin and two triplet pregnancies), there were 843 (22.7%) stillbirths with no significant difference between groups (OR 1.04, 95% CI 0.65-1.67) (Table 12).

Additional information on Maternal Outcomes

Nearly all maternal deaths (95·2%) occurred in central referral facilities. There were no significant changes in the cause of maternal death between groups (Table 13). The highest proportion of first eclamptic fits occurred in the community. After adjustments, there were no significant changes between groups in the place of first fit. Nearly half of emergency hysterectomies were performed for ruptured uterus (47.4%; n=323) with 38.2% (n=260) for postpartum haemorrhage alone. After adjustments, there were no significant changes in the cause of hysterectomy between groups (Table 13).

Table 13 Additional information on Primary Outcomes

	Pre-intervention	**Post-intervention**	**Planned Adjusted Comparison (Trend & Step)[1] (Odds Ratio)**	**Adjusted Comparison (Bent Stick)[2] (Odds Ratio)**
Place of death (as % of all deaths)	**N=451**	**N=546**		
Central referral facility: n (%)	428 (94.9%)	522 (95.6%)	-	-
Peripheral facility: n (%)	12 (2.7%)	17 (3.1%)	-	-
Community: n (%)	11 (2.4%)	7 (1.3%)	-	-
Cause of death	**N=451**	**N=546**		
Obstetric Haemorrhage: rate/10,000 deliveries n (%)	6.0 147 (32.6%)	7.3 212 (38.8%)	0.86 (0.56-1.33)	0.56 (0.29-1.05)
Pregnancy related sepsis: rate/10,000 deliveries n (%)	2.7 67 (14.9%)	2.6 74 (13.6%)	-	-
Other Sepsis: rate/10,000 deliveries n (%)	0.6 15 (3.3%)	0.5 13 (2.4%)	-	-
Hypertensive disorder in pregnancy (Eclampsia/ Pre-eclampsia/ Stroke): rate/10,000 deliveries n (%)	3.3 81 (18.0%)	4.3 123 (22.5%)	0.76 (0.46-1.25)	2.07 (0.33-13.12)
Other[3]: rate/10,000 deliveries n (%)	5.7 141 (31.3%)	4.3 125 (22.9%)	0.88 (0.62-1.24)	0.54 (0.05-5.73)
Place of first eclamptic fit	**N=1314**	**N=1378**		

Central referral facility: rate/10,000 deliveries n (%)	20.5 506 (38.5%)	11.5 333 (24.2%)	0.56 (0.33-0.97)	1.17 (0.53-2.55)
Peripheral facility: rate/10,000 deliveries n (%)	11.3 280 (21.3%)	12.6 363 (26.3%)	1.55 (1.10-2.20)	1.35 (0.17-10.45)
Community: rate/10,000 deliveries n (%)	21.4 528 (40.2%)	23.6 682 (49.5%)	1.02 (0.56-1.86)	2.78 (0.65-11.89)
Cause of hysterectomy	**N=316**	**N=365**		
Postpartum Haemorrhage: rate/10,000 deliveries N (%)	4.5 112 (35.4%)	5.1 148 (40.5%)	1.23 (0.72-2.10)	0.45 (0.11-1.09)
Ruptured uterus: rate/10,000 deliveries N (%)	6.1 151 (47.8%)	6.0 172 (47.1%)	0.87 (0.41-1.84)	0.12 (0.02-0.82)
Sepsis: rate/10,000 deliveries N (%)	0.8 21 (6.6%)	0.9 25 (6.8%)	-	-
Other[3]: rate/10,000 deliveries N (%)	1.3 32 (10.1%)	0.7 20 (5.5%)	-	-

Planned analysis of individual sites is shown in Figure 25. The event rate in the control period ranged from 39.4/10,000 deliveries in Lusaka to 324/10,000 deliveries in Freetown. After adjustment, there was considerable heterogeneity in the apparent effect in individual clusters (I^2 = 94.5%) with significant benefit shown in three sites, including the two clusters with the highest and lowest baseline event rate.

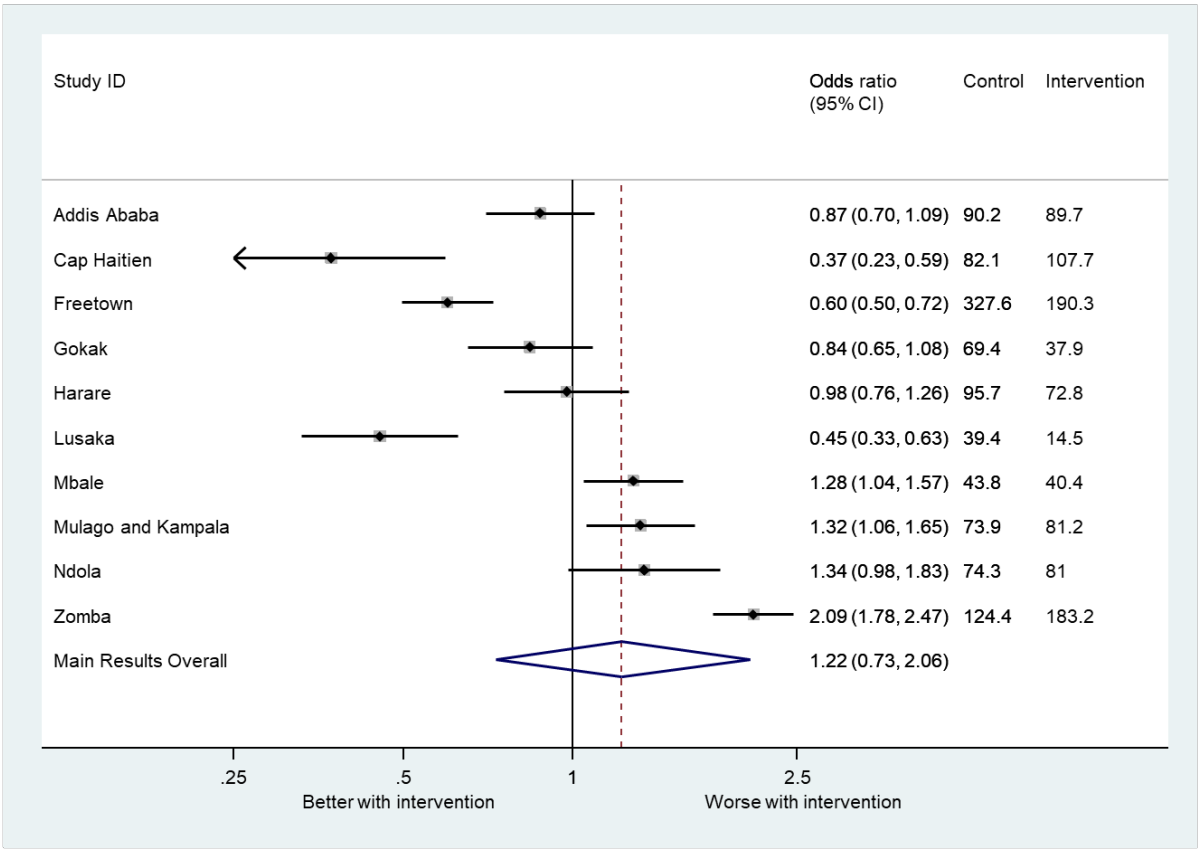


Figure 25 Forest plot of event rates in individual clusters and the effect of the intervention on the primary composite outcome analysed with fixed linear trends.

3.5 Discussion

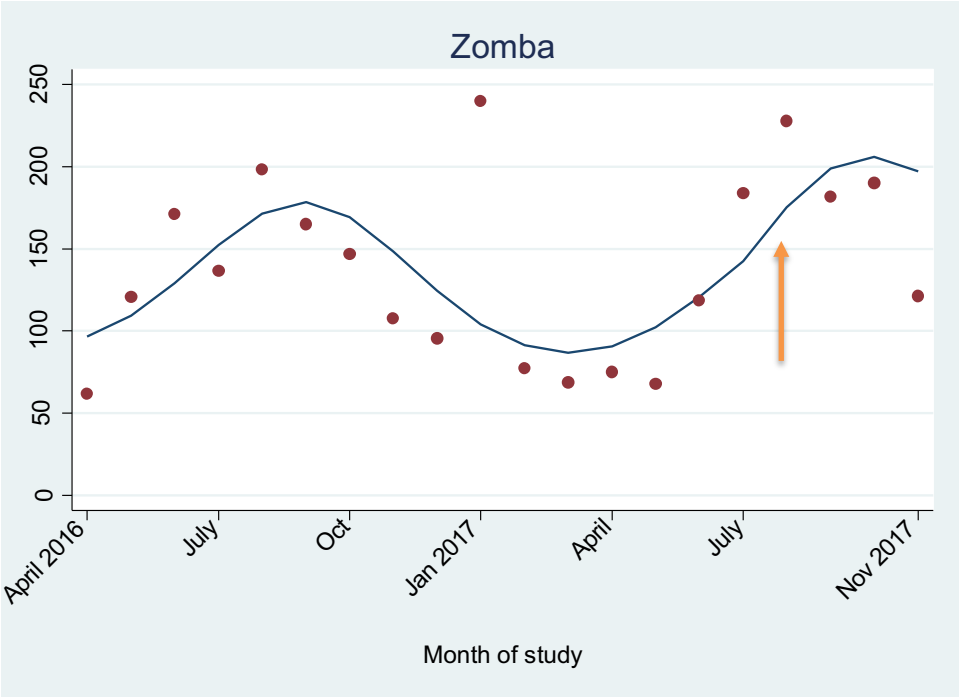
This trial was unable to demonstrate a direct effect of the CRADLE intervention on a composite outcome of maternal mortality and morbidity, although these fell by 8% during the trial. There was considerable heterogeneity of data between and within sites, giving insufficient power despite over 4000 primary events, higher than anticipated. Pre-

specified secondary analyses showed the intervention had a significant reduction in emergency hysterectomy but not eclampsia or maternal death.

The strengths of this study include the multi-country, population-based design, size of the trial population, use of routine birth and death data triangulated with active case finding, important clinical outcomes, implementation into all levels of healthcare facilities (including community) within clusters, and the randomised design. A limitation was that implementation and data collection were by the same team, introducing possible measurement bias. It is also plausible that in some clusters, use of the intervention may have resulted in greater reporting of the primary outcome if previously occurring without documentation in the community, with a bias against the intervention. However, case-finding and data collection were carefully optimised in the feasibility phase and closely monitored by the local investigator and research team.

The stepped wedge RCT design was chosen for practical reasons as phased implementation across ten clusters was more feasible than simultaneous implementation and because it would have been challenging to get sufficient cluster matching. In addition, as BP measurement is part of routine maternity care and adequate access to equipment in low-resource settings is a challenge, delivery to all clusters was deemed preferable by our sites. However, this trial design also reflects a study limitation as it is vulnerable to temporal trends and external influences, although extensive efforts were made to capture and adjust for these. The decision to involve diverse clusters across eight countries was made to enable generalisability. We have demonstrated successful intervention delivery in multiple settings. Variation between clusters was taken into account in the sample size calculation and the randomisation procedure, but there were no reliable data on which to adjust for temporal and seasonal trends. These were larger than anticipated as shown in Figure 26. This together with the size and complexity of the

temporal trends, had a substantial impact on power, despite the large total number of events.



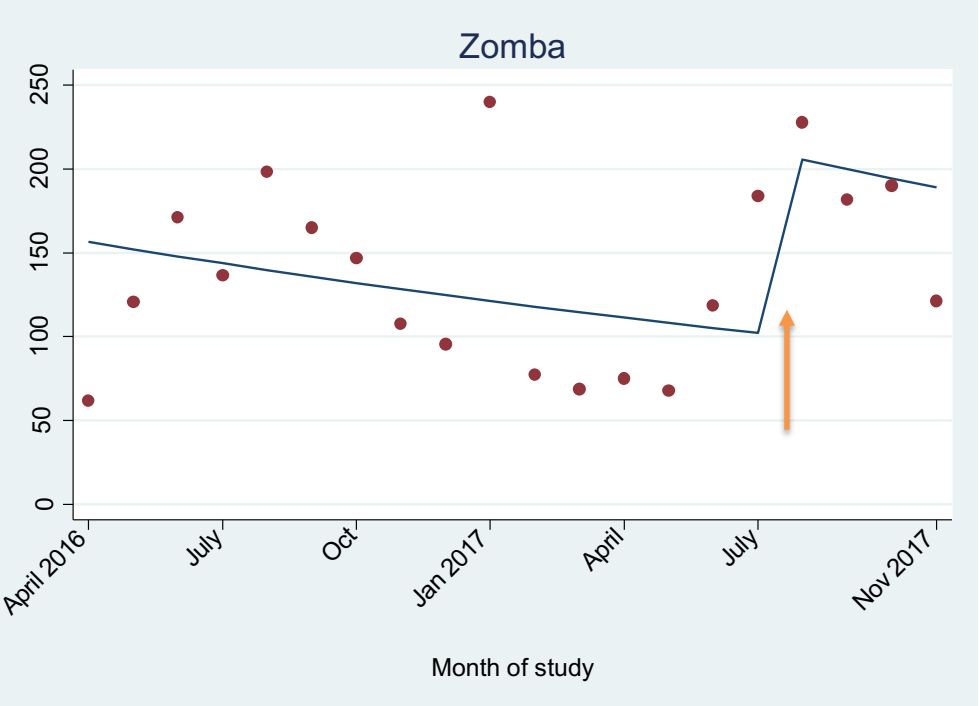


Figure 26 Analysis of primary outcome in Zomba analysed by trend and step (Panel A) and accounting for seasonality (Panel B).
Arrow denotes time of implementation

Although stepped wedge RCTs are increasingly popular,(Kristunas et al., 2017, Martin et al., 2016) this trial was unusual in being undertaken across multiple countries and presents valuable learning for others planning multi-country stepped wedge RCT; we can only identify one published trial undertaken in multiple countries (Europe).(van der Kooi et al., 2018) Compared to parallel-cluster trial designs, stepped wedge RCTs remains an appropriate solution with an ICC anticipated up to 0.1,(Hemming et al., 2015) but the potential variation between clusters (and logistical challenges) are magnified when the study involves multiple countries.

Across all our sites, there was an 8% reduction in the primary outcome during the trial period. The statistical analysis accounts for event rate trends in each cluster before and after the intervention. After adjusting for these, this reduction cannot be directly attributed to the intervention. Trends from the WHO indicate that over the last five years, the average reduction in MMR across the eight countries in this trial was only 2% per year (range -1% in Malawi to 22% in Ethiopia).(World Health Organisation, 2015b) There is a scarcity of reliable prevalence trends for eclampsia and maternal morbidity in these countries as data are primarily limited to intervention studies or small observational studies. It is plausible that the intervention was beneficial but not proven by our trial design or that participation in the trial and the process of data collection was associated with benefit.(McCarney et al., 2007)

Behavioural change theory states that to be effective, interventions should target specific behaviours and that success is dependent on having the necessary skill and intention, in the absence of environmental constraints.(Fishbein, 2000) The CRADLE intervention incorporated the device with an educational package and clinical champions to promote the importance of vital signs measurement in pregnancy. We hypothesised that this would improve the quality of care by promoting task-sharing, improving skill and

providing reliable equipment thus increasing the number of women that receive vital signs monitoring and subsequent management of pregnancy complications. Following identification of complications, prevention of morbidity and mortality is dependent on capacity of HCP and their health system to respond. A mixed-methods process evaluation was undertaken in parallel to this trial. This measured implementation (fidelity, dose and reach) and explored potential mechanisms of the intervention in each cluster. A second paper presents these results and explores whether these measures, in combination with staffing and resource levels, impact on the effect of the intervention in different clusters.

In conclusion, the CRADLE intervention was successfully implemented into routine maternity care in low-resource settings. This was associated with a reduction in a composite of death, eclampsia and hysterectomy but only the latter was directly attributed to the intervention. The trial had insufficient power due to unexpected variation between clusters and despite more than 4000 primary outcome events, which was higher than anticipated. This should be taken into consideration in planning future stepped wedge RCT. Effects on individual sites and components of the primary outcome in relation to availability of resources and staffing needs investigation.

4 Exploring the effect of implementation and context on a stepped wedge randomised-controlled trial of a vital sign triage device in routine maternity care in low-resource settings

4.1 Abstract

Background:

Interventions aimed at reducing maternal mortality are increasingly complex. Understanding how complex interventions are delivered, to whom, and how they work is key in ensuring their rapid scale up. We delivered a vital signs triage intervention into routine maternity care in eight LMIC countries with the aim of reducing a composite outcome of morbidity and mortality. This was a pragmatic, hybrid effectiveness-implementation SW-RCT. In this study, we present the results of the mixed-methods process evaluation. The aim was to describe implementation and local context and integrate results, to determine whether differences in the effect of the intervention across sites could be explained.

Methods:

The duration and content of implementation, uptake of the intervention and its impact on clinical management were recorded. These were integrated with interviews (n=36) and focus groups (n=19) at three-months and six to nine-months after implementation. In order to determine the effect of implementation on effectiveness, measures were ranked and averaged across implementation domains to create a composite implementation strength score and then correlated with the primary outcome.

Results:

Overall, 61.1% (n=2747) of health care providers were trained in the intervention (range 16.5% to 89.2%) over a mean of 10.8 days. Uptake and acceptability of the intervention was good. All clusters demonstrated improved availability of vital signs equipment. There was an increase in the proportion of women having their BP measured in pregnancy following the intervention (79.2% vs. 97.6%; OR 1.30, 95% CI 1.29-1.31) and no significant change in referral rates (3.7% vs. 4.4% OR 0.89; 95% CI 0.39-2.05). Availability of resources and acceptable, effective referral systems influenced health care provider interaction with the intervention. There was no correlation between process measures within or between domains, or between the composite score and the primary outcome.

Conclusions:

This process evaluation has successfully described the quantity and quality of implementation. Variation in implementation and context did not explain differences in effectiveness of the intervention on maternal mortality and morbidity. We suggest future trials should prioritise in-depth evaluation of local context and clinical pathways.

4.2 Background

Despite recent advances, 800 women die every day in pregnancy and childbirth, 99% of which are in LMIC.(World Health Organisation, 2015b, Say et al., 2014) The leading causes of death are haemorrhage, hypertensive disorders and sepsis,(Say et al., 2014) the majority of which can be prevented with established, cost-effective interventions.(Adam et al., 2005) Yet, in LMIC, challenges such as inadequate numbers of trained HCP (World Health Organisation, 2006) and insufficient access to reliable, accurate, equipment to monitor vital signs (Abdu et al., 2017, Penfold et al., 2013, Ziraba et al., 2009, Ministry of Health and Social Welfare Tanzania, 2014-2015) lead to delays in identifying women with pregnancy complications which contributes to preventable

mortality and morbidity.(Thaddeus and Maine, 1994, Gabrysch and Campbell, 2009) Current priorities of the global health community include combining single effective interventions into packages of care, alongside strategies to improve uptake, coverage and sustainability of these interventions.(Campbell and Graham, 2006, Betrán et al., 2018)

The success of any intervention is dependent on its use in a specific environment and population.(Victora et al., 2011) Understanding the most effective routes to deliver these complex interventions and how they may work in varying local contexts is key.(Peters et al., 2013a) RCT are often criticized for providing little information about why and how an intervention worked (or not) and the context within which it was delivered.(Grant et al., 2013, Glasgow et al., 2003) This limits the reproducibility of findings. Where interventions are shown to be ineffective, a trial report may not explain whether this is due to poor implementation, leading to potentially sound interventions being rejected. Knowing which components of an intervention and their delivery, are necessary to produce an effect in a certain population is vital for results to be reproduced, adapted or scaled-up. This is of even greater importance in low-resource countries where the burden of disease is so great.

Guidance exists on how to evaluate implementation alongside effectiveness,(Peters et al., 2013a, Peters et al., 2013b, Moore et al., 2015) integrating mixed-methods to evaluate how well an intervention was delivered, to whom, in which context and how it may work.(Moore et al., 2015) Hybrid effectiveness-implementation trials aim to evaluate implementation alongside effectiveness.(Curran et al., 2012) Whilst this methodology is established in evaluation of health promotion and public health interventions, its application in maternal health in low-resource settings is scarce (Gimbel et al., 2016) and few studies are planned.(Chavane et al., 2014, Utz et al., 2017, Ridgeway et al., 2015, Kikuchi et al., 2015, Maru et al., 2018)

The CRADLE-3 trial was a pragmatic, stepped-wedge RCT of a novel vital signs device and training package introduced into routine maternity care, in ten clusters across Ethiopia, India, Haiti, Malawi, Sierra Leone, Uganda, Zambia and Zimbabwe with the of aim reducing a composite outcome of maternal death, emergency hysterectomy and eclampsia (Nathan et al., 2018b). The trial was accompanied by a nested mixed-method process evaluation which was informed by the MRC guidance for complex interventions (Moore et al., 2015). The CRADLE VSA accurately measures BP, HR and calculates SI (de Greeff et al., 2008, Nathan et al., 2015b, Nathan et al., 2015a, Nathan, 2018) and displays results on a traffic light EWS.(Nathan et al., 2018a) This is important in LMIC where routine clinical tasks, such as vital signs measurement, are often undertaken by those with minimal training and community health workers also play a vital role in maternity care, often being the first point of contact and an essential link to clinical services.(Campbell and Graham, 2006, Schneider et al., 2016)

It was hypothesised that better availability of equipment would improve the efficiency and capacity of HCP to monitor vital signs. It was also hypothesised that training would improve HCP understanding of when and how to measure vital signs and how to identify and manage pregnancy complications. The ease of use of the CRADLE VSA and the traffic light EWS would mean that all cadres of HCP would be alerted to abnormal vital signs. Together, this would result in more women receiving more vital signs measurements, so abnormal results would be identified earlier and managed faster, thus reducing maternal morbidity and mortality. These hypotheses were developed through field studies, stakeholder engagement and literature demonstrating need for improved access to equipment,(Abdu et al., 2017, Penfold et al., 2013, Ziraba et al., 2009, Ministry of Health and Social Welfare Tanzania, 2014-2015) training in detection and management of pregnancy complications,(Harvey et al., 2004, McCaw-Binns, 2004, Boene et al., 2016) and task-sharing in maternity care in low resource settings.(World

Health Organisation, 2005b, Fulton et al., 2011) In addition, qualitative evaluation (Nathan et al., 2018a) and a mixed-methods feasibility study (Vousden et al., 2018) determined that the device is robust and easy to use by any cadre of HCP and that the training package and implementation strategy were acceptable and had potential to impact on clinical management (escalation and referral). A logic model was created to present these assumptions, processes and anticipated outcomes (Figure 22 on page 121). This informed the key areas for evaluation in this study.

Our aim was to describe the implementation of the intervention and the local contexts in which it was delivered and to determine whether differences in the effect of the intervention on the primary outcome can be explained. This can be divided into a several objectives informed by the RE-AIM framework.(Gaglio et al., 2013, Grant et al., 2013) These were chosen with the aim of exploring if and how this pragmatic intervention impacted on routine maternity care in a wide variety of settings:

- To evaluate whether the intervention was implemented as outlined in the protocol by describing the quantity and quality of training in each setting.
- To determine the reach of the intervention by evaluating the extent to which health care professionals and women were exposed to the intervention.
- To explore how the intervention was adopted into routine maternity care, whether this changed over time and the potential sustainability of this.
- To explore differences in context, implementation, reach and adoption between sites and determine whether they can explain differences in the effect of the primary outcome in different settings.
- To explore if and how the intervention impacted on routine maternity care across the facilities in each setting and identify possible reasons for this.

4.3 Methods

Intervention

The intervention comprised the CRADLE VSA which was delivered through a one-off interactive training session of CRADLE Champions. These were purposely selected HCP from each ward or facility in the trial cluster. They were selected prior to implementation, either as managers and/or as influential in their clinical area by the local research team. Interactive training sessions covered the use and maintenance of the device and suggested clinical management in response to abnormal vital signs using presentations, demonstration, practice and clinical scenarios. The CRADLE Champions were provided with posters, training manuals and a short, animated training film (sent by Bluetooth to smartphones). The CRADLE Champions then used these materials to provide ongoing training and support in their clinical area. These components of the intervention and implementation were developed during a six-month feasibility phase with input from stakeholders.(Vousden et al., 2018) The local research team continued to provide regular support to all facilities with at least monthly contact. Existing equipment for measuring vital signs was usually removed from clinical use, unless it had a specific function such as automation for high dependency. This intervention was compared to routine maternity care using locally available medical devices and management guidelines.

Design and Setting

Each cluster comprised at least one urban or peri-urban, secondary or tertiary health facility that provided comprehensive emergency obstetric care, with multiple peripheral facilities that refer to the central hospital.(Nathan et al., 2018b) The stepped-wedge design meant that clusters crossed over from control to the CRADLE intervention in one of nine steps at two-monthly intervals over the 20-month trial duration. The order of steps

was randomly allocated using a computer-generated sequence.(Nathan et al., 2018b) This design was chosen to minimise the risk of bias and show causality, should a significant effect of the intervention be demonstrated.

Population

All HCP working in maternity care in the cluster facilities had access to the intervention, including community HCP in two clusters where they were active in routine maternity care and approved for inclusion (Ndola and Cap Haitien). All women identified as pregnant or within 42 days of delivery, that presented to routine maternity care, were exposed to the intervention without exclusion.

Outcomes

The primary outcome was a composite of at least one of maternal death, eclampsia or emergency hysterectomy per 10,000 deliveries. The implementation and impact of the intervention in each site was evaluated by mixed-methods under three implementation domains as shown in Figure 27, informed by the RE-AIM framework.(Proctor et al., 2011, Grant et al., 2013, Moore et al., 2015) We identified potential ways in which the intervention may be working, and the necessary resources and actions required for this, then selected measures that were important but feasible to collect within this pragmatic, multi-centre trial design.(Vousden et al., 2018)

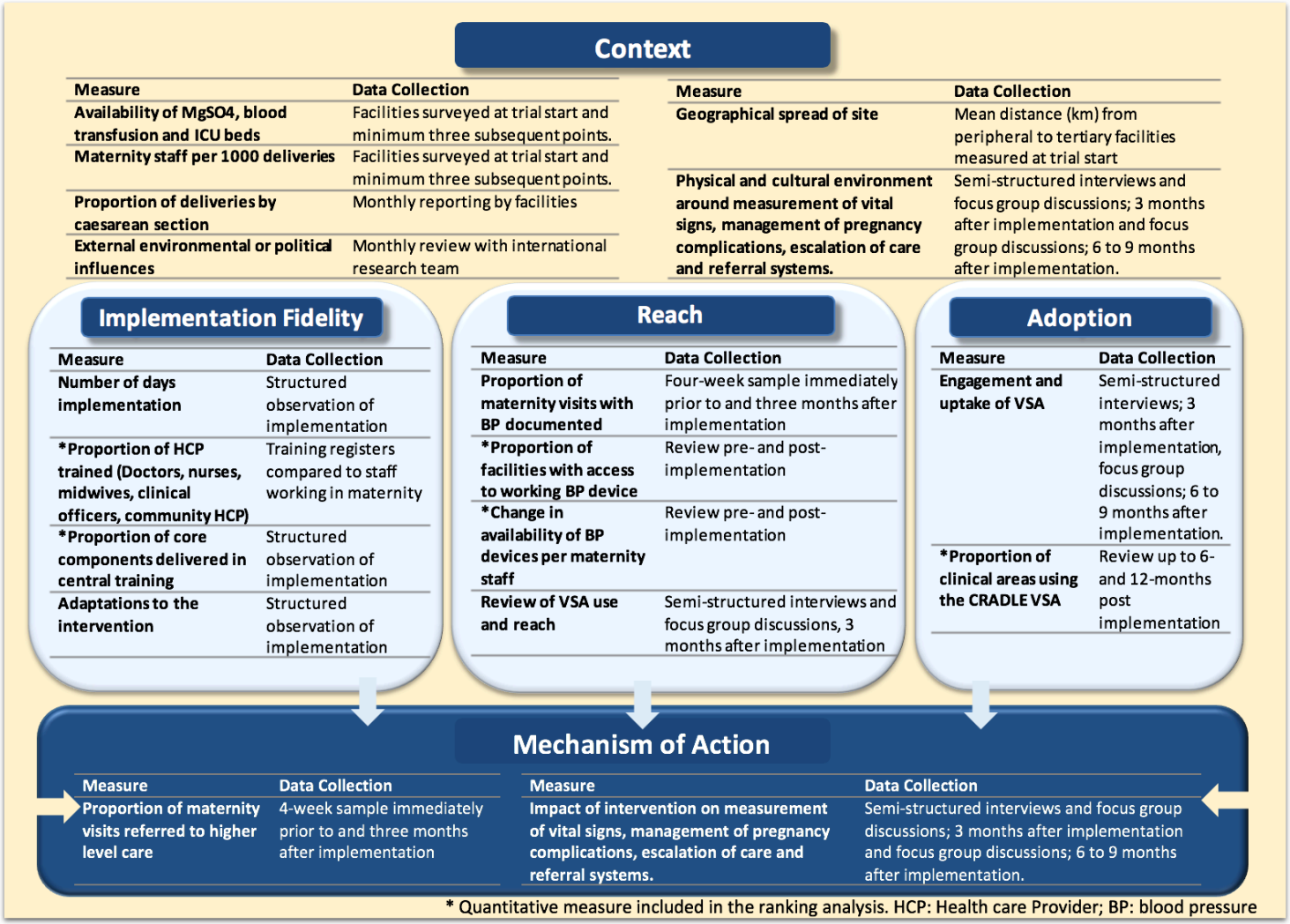


Figure 27 Implementation domains and of data collection methods

Data Collection

Baseline data were collected from each facility on the distance from the nearest tertiary referral hospital, number of HCP working in maternity (doctors, nurses, midwives, clinical officers and community HCP in Ndola and Cap Haitien), availability of existing BP equipment, blood transfusion services, intensive care beds and magnesium sulfate. These were selected as markers of health system context that were important and feasible to measure. This was updated a minimum of three times during the trial period. Major changes to the political or physical environment such as infrastructure, staff retention and extreme weather conditions were evaluated monthly. The number of deliveries in each cluster was collected by review of facility registers and routine reporting. Community deliveries were captured through a variety of methods such as household visits from community health workers in India and monthly reporting meetings with traditional birth attendants in Haiti (three sites did not routinely record deliveries that occur outside of facilities).

Training was observed against a pre-defined observational checklist, including the number of training days and the proportion of core content delivered. Training registers were completed and compared to staffing numbers. All clusters reported at six-monthly intervals on the proportion of clinical areas using the CRADLE VSA device. In order to evaluate the ways in which the intervention, and participants interaction with it, may trigger change (mechanisms of action),(Vousden et al., 2018) the number of women attending maternity services, the proportion that had their BP measured and the proportion referred to higher level care were measured for a four-week period immediately prior to implementation and three months after implementation. This was integrated with qualitative findings on context and use of the device.

In each site, we undertook semi-structured interviews (n=3-5) and focus group discussions (n=1) with HCP, three months after implementation. These explored the uptake of the intervention, its influence on clinical management and any unexpected consequences. In sites that implemented in the first 14 months of the trial, a further focus group discussion was undertaken at six to nine months after implementation to explore whether influence on clinical management, escalation and referral systems changed over time and the sustainability of the intervention. In total we conducted 36 interviews and 19 focus group discussions with 130 participants across the ten sites. Participants were selected through purposive sampling to ensure representation of different HCP cadres and facilities. Participants were approached face-to-face and gave written informed consent. These were recorded and transcribed verbatim and field notes were recorded. Content and notes were reviewed iteratively to identify further participants until data saturation was achieved. All qualitative work was undertaken, translated and transcribed by experienced local research coordinators (with a clinical background) following training from the trial coordinator and senior social scientist (JS) or qualitative researchers. Researchers had limited prior relationship with the participants. Two data coders that were independent to the interviewers undertook initial analysis using QSR NVivo 11 software (QRS, Vic, Australia) prior to revealing the analysis of the primary outcome and then further analysis once the results were known. We used the framework method with a coding framework that drew upon the study objectives, logic model and interview guide.(Ritchie J, 2003., Gale et al., 2013) New concepts initiated by participants that could not be categorized were coded using an inductive approach.(Tong et al., 2007)

In order to compare implementation and determine whether this was related to effectiveness, we used a ranking approach as previously described in other fields.(Wilson et al., 2010, Fretheim et al., 2006, Farris et al., 2007) Clusters were ranked from highest to lowest on selected quantitative outcomes on implementation fidelity, reach and adoption (marked * Figure 27). These were selected as the direction of benefit

was clear, whereas the anticipated direction of change for outcomes on context and action were less clear (e.g. poorer availability of resources at the trial start may be associated with greater benefit from the intervention due to greater need, or less benefit due to inability to respond to abnormal vital signs). Outcomes under the same domain were averaged and converted to a possible range (0 to 1) to give each cluster a score for each domain analysed (implementation fidelity, reach and adoption). These were then averaged to give each cluster a single composite score reflecting their implementation (possible range 0-1).(Wilson et al., 2010, Fretheim et al., 2006, Farris et al., 2007) Due to the stepped wedge design, the single measure of adoption was only available in eight of the ten sites. The individual domain scores and overall composite score were compared to primary outcome in each site. Correlation between the individual measures within domains was also determined.(Ryman et al., 2011)

Statistical Analysis

Statistical analyses were undertaken in Stata version 14.2. For the primary outcome in individual sites, the main analysis used logistic regression with generalised estimating equations and a population-averaged model. Adjustments were made for fixed centre effects (categorical) and separate fixed linear trends (continuous) in each centre to account for changes in the primary outcome over time.(Hussey, 2007) Results are reported as ORs. Details of randomisation and further analysis of the trial are published in protocol (Nathan et al., 2018b) and primary results paper.(Vousden, 2019) For the evaluation of implementation, the ranks were summarised, and simple rank correlations calculated. We used meta-regression to see if the primary outcome in individual sites were related to the individual and composite implementation scores.(Knapp and Hartung, 2003) For comparison of referral rates before and after implementation, unadjusted OR were calculated and combined using random effects meta-analysis.(DerSimonian and Laird, 1986) In each site a four-week period immediately

prior to and three months after implementation were compared, this is a non-randomised comparison

4.4 Results

Implementation Fidelity

The average duration of implementation training across all facilities was 10.8 days (range 7 days in Addis Ababa to 18 days in Mbale). In total, 2747 HCP were trained, 61.1% of all those working in maternity services in those sites (range 16.5 in Kampala, Uganda to 89.2% in Zomba, Malawi, Table 14). Nine of the ten sites delivered all the key content of training. Freetown, Sierra Leone was the first to implement with less emphasis on training senior staff, the background of device development and validation studies. Following challenges from senior staff in accepting device accuracy, this was emphasised in subsequent site training.

Table 14 Quantitative implementation measures of implementation fidelity, reach and adoption

	Implementation	**Reach**					**Adoption**			
Site	Staff trained in roll out period	Proportion of women with BP measurement pre-intervention[ψ]	Proportion of women with BP measurement post-intervention[ψ]	Unadjusted Comparison	Facilities with working BP pre-intervention	Facilities with working BP post-intervention	Clinical areas using solely VSA at 6 months	Clinical areas using VSA with other devices at 6 months	Clinical areas using solely VSA at 12 months	Clinical areas using VSA with other devices at 12 months
	N (%)	N (%)	N (%)	OR (95% CI)	% (devices: HCP)	% (devices: HCP)	%	%	%	%
Addis Ababa	192 (36.9%)	-*	-*	-*	100% (1:3)	100% (1:2)	33.3%	66.7%	[υ]	[υ]
Cap Haitien	189 (73.5%)	-*	-*	-*	100% (1:3)	100% (1:3)	76.2%	23.8%	[υ]	[υ]
Freetown	243 (57.9%)	2199 (87.7%)	3335 (100%)	1.14 (1.12-1.16)	84·6% (1:13)	100% (1:4)	73.1%	26.9%	96.2%	0.0%
Gokak	297 (87.1%)	-*	-*	-*	97·5% (1:1)	100% (1:0.7)	72.3%	27.7%	[υ]	[υ]
Harare	405 (69.9%)	-*	-*	-*	92%	100%	[υ]	[υ]	[υ]	[υ]

					(1:12)	(1:5)				
Kampala	188 (16.5%)	-*	-*	-*	92.3% (1:19)	100% (1:4)	33.8%	47.9%	34.2%	47.9%
Lusaka	265 (33.9%)	-*	-*	-*	100% (1:10)	100% (1:5)	75.9%	24.1%	υ	υ
Mbale	314 (59.2%)	4640 (42.6%)	11300 (96.2%)	2.26 (2.21-2.31)	92% (1:5)	100% (1:2)	87.3%	9.9%	υ	υ
Ndola	349 (86.6%)	5673 (98.2%)	5782 (100%)	1.02 (1.0-1.2)	93.5% (1:7)	100% (1:2)	90.2%	9.8%	90.2%	9.8%
Zomba	305 (89.2%)	11860 (88.4%)	10783 (94.1%)	1.06 (1.06-1.07)	100% (1:17)	100% (1:2)	υ	υ	υ	υ
Total/Mean	**2747 (61.1%)**	**6093 (79.2%)**	**7800 (97.6%)**	**1.30 (1.29-1.31)**	**95% (1:9)**	**100% (1:3)**	**73.1%**	**23.3%**	**73.5%**	**20.0%**

*data not recorded

υ Data not available due to stepped wedge trial design (time point exceeded trial duration)

ΨRecorded for a one-month period immediately prior to implementation, and a one-month period three months after implementation.

Educational materials were translated (India, Ethiopia, Malawi, Haiti) and delivery was adapted to take into account locally available medications and referral structures. In India, all training was delivered by the research team rather than via CRADLE champions (87.1% trained). In Haiti, community HCP without formal training had a longer duration of training (approximately 2 days), spending more time checking understanding. The duration of training was longer in sites with a wider geographical spread or more challenging terrain (Mbale, Uganda; 18 days and Zomba, Malawi; 16 days) except in India, who were able to mobilise a larger local research team (10 days). External events influenced implementation in two sites. One of three tertiary hospitals in Cap Haitien, Haiti was closed at the time of implementation due to strike action, therefore key managers were trained, and remaining staff received training within two weeks of opening. In Ndola, Zambia implementation coincided with roll-out of alternative (un-related) training for some maternity staff by the Ministry of Health. Implementation went ahead as planned for remaining staff and those that were unable to attend were trained by champions or the research team in the subsequent week.

Clusters that trained fewer staff tended to have multiple, very large facilities with high numbers of deliveries (Lusaka and Kampala), except Freetown, which was a smaller unit but trained fewer staff. This cluster was the first to implement, possibly demonstrating the learning curve of the research team. Qualitative findings demonstrated that the majority of participants from all sites felt the training was adequate (Demographic details of the qualitative participants are shown in Table 15. Champions felt confident using the materials to orientate their colleagues. Recipients of training from champions were confident to use the VSA and also to orientate others. A small minority of participants from the three sites that trained the fewest HCP (Addis Ababa, Kampala and Freetown) highlighted that training from the champions had been brief, that staff who were not trained took longer to learn and faced initial challenges with use, or that ongoing training

may not be sustainable with staff turnover (quotes to illustrate in Table 16).

Table 15 Demographic details of interview and focus group participants

	Interview Participants	**Focus Group Discussion Participants**	**Focus Group Discussion Participants**
Time after implementation	Three-months	Three-months	Six to nine months
Mean duration (minutes)(range)	25 (7-45)	64 (39-125)	58 (35-87)
Profession			
Midwife	16	38	28
Nurses	13	23	18
Doctors	3	2	4
Clinical Officers	0	1	0
Community HCP	1	4	5
Allied HCP	3	2	5
Gender			
Male	5	7*	7
Female	31	57*	53
Age (years)			
18-24	2	0*	0
25-34	12	24*	20
35-44	14	31*	23
45-54	6	7*	8
55-65	2	2*	9
Educational Level			
Secondary or less	2	8*	6
Diploma	27	47*	30
Certificate	2	5*	11
Bachelor's Degree or higher	5	4*	13
Experience (years)			
1-5	12	16*	15
6-10	8	17*	13
11-15	9	16*	14
>15	7	15*	18

Table 16 Selected quotes to illustrate qualitative themes

Domain	Theme	Qualitative Quote
Fidelity	Quality of training	*Midwife, Tertiary Hospital, Ndola, Zambia: "Sister* who had an opportunity to attend the one-day workshop where the orientation was done (on) how to use the BP machine and she is the one who disseminated the information, orientated myself and other midwives from labour ward on how to use this BP machine… after I got used I haven't had any problems and I have also oriented other medical personnel on how to use it. It has been so helpful."*
		Midwife, Clinic, Addis Ababa, Ethiopia: "The apparatus is very good. But there was a minor problem. None of us took any training, but instead we just received the apparatus and we started putting it to use. And it had some problems on accuracy."
Reach	Better availability of equipment meant more measurements done and on more women.	*Clinical Officer, Peripheral Hospital, Zomba, Malawi: "it's just a matter of having enough resources now, that at least we have a BP machine in the ward and outside to the health centres, and indeed is the easy one, is the fast one. So this is what can take at the same time to listen to the BP. So the things I see at least is that the BP are taking place more often, because the BP machine is always available"*
	Better availability of equipment reduced time taken to monitor.	*Midwife, Outpatients, Tertiary Hospital, Freetown Sierra Leone: "…with one referral the pressure was down, it prompted us greatly, to start IV fluids, call a doctor to come back from theatre...(details of clinical management). This machine (VSA) helped us a lot because if it was any other machine where we use stethoscope, we would have needed to run around trying to look for it, but that machine is already there. That morning the machine saved her, because thank god she survived, was discharged, and we are happy about that."*
	Increased confidence resulted in increased monitoring in facilities	*Medical Officer, Primary Health Centre, Gokak, India: "Earlier, because of overload of work our ANMs were not checking the BP with mercury apparatus. Now, after introduction of this machine and after showing this to AHSAs also in a meeting, they are happy with what they are doing. And they are doing more checks than they were doing earlier. Earlier, they were sending pregnant women to the doctor, telling*

		them that the doctor will check the BP. But now they are also checking and then sending the patients to me."
	Task-sharing increased monitoring in communities	*Registered Nurse, Clinic, Ndola, Zambia: "…we had a case last month where a SMAG member (Safe Motherhood Action Group volunteer) got BP machine to go and visit a woman in one of the villages and she discovered that BP was high and client referred and managed at Ndola Central Hospital. Without Cradle that woman would have been left to die in the community. The Cradle VSA machine is helping us a lot."*
Adoption	Ease of use	*Junior midwife, Clinic, Addis Ababa, Ethiopia: "In our health centre, the former device used to fail often. This one measures both the blood pressure and pulse. This means it helps us forecast to the future, about the condition of the woman. Before this, we used to measure only blood pressure, and that's it. But now since it helps us forecast her pulse. It assesses the condition of the woman, whether she is entering a danger zone or not. It helps us to take care of the mother before the event. Second, since it helps us with the management during the emergency case, it prepares us to take action immediately. So, it guides us, it measures pulse and as long as we follow the rules of positioning, its accuracy is also very good. I like it."*
	Improved reliability and champion/research team support	*Midwife, Clinic, Addis Ababa, Ethiopia: "The devices we used before were very prone to malfunctioning. But if this one malfunctions, it is often due to improper usage. When such problems happen call (the research assistant) and try to solve the problems. In general, it is helpful for our health centre."*
	Security	*Midwife, Labour Ward, Tertiary Hospital, Ndola, Zambia: "Yes we had one experience. I think they were just introduced. One blood pressure machine had gone missing…And from that time we learnt a lesson. So each time we are changing shift all the equipment is put on the table and handed over."*
Mechanism of action	Cultural change	*Nursing officer, Clinic, Mbale, Uganda: "it has become a quality issue to monthly charts on how many patients had their BP taken each month since machines are readily available for use. It has increased the work load since every mother has to have her BP taken."*
	Alerts trigger increased investigation	*Maternity Health Assistant, Clinic, Freetown, Sierra Leone "…we check them all when they come and if I see those colours I call my boss. Because when the machine shows those colours it's a problem and we need to ask her some questions. And if she says she's not well I can say there is something wrong with her. It will not show this colour if they are well. A person who is well will show a green colour. And if it still*

		persists for two or three times with that colour, we can send them to do tests sometimes to detect anaemia, sometimes (haemoglobin) 9 grams or 8 grams. So we can treat her little by little."
	Alerts aid communication	*Midwife, Private Labour Ward, Ndola, Zambia: "as a midwife, as nurse you are supposed to know the abnormal so because of that at least it has…I wouldn't say it has changed (management) much but sometimes yes it does help us. When it is red we do the BP we check again, if its red it means the BP is very high we have to inform the doctor immediately. So there are times when you would call the doctor and they not in, you make sure you emphasize because that the patient has to be seen soon.."*
	Alerts convince women and families	*Midwife, Clinic, Ndola, Zambia: "if it shows red, I also explain to her even showing her to say "have you seen this colour? Where is this arrow pointing, no it is pointing up. Yes, this means am supposed to refer you to Ndola central" but like before when we were using the digital and the mercury we would just do and even if the patient reads the readings to be high (they) would not understand. But this time around since it has colours, even for somebody who is not learned, it is easy to convince them"*
	Alerts motivate women	*Auxiliary Nurse Midwife, Community Health Post, Gokak India: "The number of those who come themselves voluntarily has increased and the awareness of getting the BP checked has improved among them. If we show them the reading, they think "Yes, all such things are there in the BP; we need to get checked; if it shows yellow it means this; if it shows red it mean this, there are the signals for us"."*

Reach

Overall, 3868 devices were delivered across 286 facilities. Four clusters recorded the proportion of women with BP measurement. All demonstrated a significant increase in measurements made after the intervention (usual care mean 79.2% (n=6093/7693) vs. intervention 97.6% (n=7800/7992); OR 1.30, 95% CI 1.29-1.31); Table 14). Prior to the intervention, 95% of facilities had access to at least one working BP machine. After the intervention, 100% had access, with better availability per HCP in all clusters. Participants from both clinics and hospitals in every cluster except Haiti, reported an increase in availability of equipment. The availability of equipment, and its ease of use, meant that more vital signs measurements could be done and faster, as staff did not spend time looking or waiting for equipment (Table 16).

Many participants reported that students and other allied HCP or volunteers would regularly help to take vital signs measurements with the device. More junior staff also took more vital signs measurements, where they would previously have referred the patient to other HCP for routine monitoring. This was reported to be due to greater confidence in their capacity to measure BP and interpret results. It was frequently commented that this made it more likely that women would have their vital signs measured (Table 16). In Haiti and Ndola, community HCP reported confidence and pride in being equipped and skilled to monitor vital signs in their community. This also led to more vital signs measurement in the community and earlier detection of abnormalities (Table 16). A minority of HCP reported that demand still outweighed supply, even though this was improved.

Adoption

The majority of sites reported rapid use of the device on all pregnant women. The reasons for rapid adoption differed according to site context. Sites with poor availability or poor-quality existing equipment (e.g. Kampala, Freetown, Mbale and Zomba) reported

rapid use, irrespective of the different proportion of staff that were trained. Sites with adequate availability of equipment prior to implementation (Gokak and Addis Ababa) elected to use the VSA in preference to other equipment citing ease of use, better accuracy and easier interpretation due to the traffic light alert which reduced the workload. This was true across all cadres of HCP from community volunteers to medical officers in hospitals.

Due to the stepped-wedge design, eight clusters reviewed use at six months post-implementation and three at 12 months. The majority of clinical areas were using solely the CRADLE VSA device at six months (73.1%; range 33.3% in Addis Ababa, Ethiopia to 90.2% in Ndola, Zambia, Table 14). Only 4.8% of clinical areas had chosen to use previously existing vital signs devices in preference to the CRADLE device. This was still reflected at 12 months (73.5% using solely the CRADLE device). A minority of sites reported barriers to adoption, the most frequent was the sensitivity of the VSA to movement and positioning, in some cases leading to mistrust of the accuracy of results. This was reported more frequently in sites with low fidelity (Freetown, Kampala and Addis Ababa). However, qualitative findings in Freetown suggest that active support from the champions or the research team resolved this concern, and this correlated with improved adoption compared to Addis Ababa and Kampala and over time (Table 14).

By the trial end, 4·6% (n=180) of VSA were reported to be broken. The most commonly reported reasons were failure of the battery, leaking of the valve in the pump or tears in the cuff. Many sites noted it was more robust than pre-existing equipment (Table 16). Very few CRADLE VSA were reported missing by the trial end (0·6% (n=23). Sites described self-directed systems of handover or registration to minimise this risk (Table 16).

Relationship with Clinical Outcome

The effect of the intervention on the primary outcome is shown in Figure 25 on page 156. After planned adjustment for temporal trends, significant benefit of the intervention was shown in Freetown, Cap Haitien and Lusaka, which included the sites with the lowest and highest baseline primary outcome event rate (39.4/10,000 deliveries in Lusaka; 324/10,000 deliveries in Freetown). There was also considerable variation in the implementation, reach, adoption and context between clusters with no significant correlation between the individual measures within any domain, including physical context. There was no significant correlation between the randomised order of implementation and the primary outcome.

The two clusters that trained the highest proportion of staff with the highest content as planned in the protocol (fidelity) were Gokak and Zomba. There was no correlation between fidelity and effectiveness (OR 0.55; 95% CI 0.19-1.55). The two sites that had the best improvement in availability of equipment (reach) were Freetown and Kampala. Overall, no correlation was demonstrated between reach and effectiveness (OR 0.62; 95% CI 0.27-1.42). The majority of facilities were using the CRADLE VSA device either alone or in combination with another device at 6 months and this measure (adoption) was not correlated with the primary outcome (OR 1.40; 95% CI 0.64-3.04). When domains were aggregated into a composite score, the combination of fidelity, reach and adoption was not significantly associated with the primary outcome (OR 0.93; 95% CI 0.07-13.01).

Context and Mechanism of action

Across all clusters an average of 50.0% of deliveries occurred in the central referral facilities (mean=1358 per month per cluster), 45.7% in peripheral facilities (mean=1241 per month per cluster) and 4.3% at home (mean=118 per month per cluster from seven clusters where this was systematically collected; Table 17). The mean proportion of deliveries by caesarean section was 17% (n=91158/536,223; range 9-31%). The

availability of key obstetric resources and staffing levels are shown in Table 17. In the majority of sites, one staff member (or less) per 1000 deliveries per month joined or left the workforce in each cluster. Availability of magnesium sulfate and blood transfusion services changed in less than 2% of facilities per month in all clusters. The measures of physical context were variable between and within sites. Lusaka, Zomba and Kampala had the fewest total staff per 1000 deliveries. The lowest proportion of caesarean deliveries were done in Lusaka (9%) and Ndola (10%). Ndola also had the lowest proportion of facilities with blood transfusion capacity (6.5%) and Cap Haitien had the fewest facilities with magnesium sulfate (25%). There were a number of external influences during the trial period, for example strike action in Kampala, Uganda and an earthquake outside of the research area in Haiti. However, sites reported minimal impact of these events on care provisions.

Table 17 Description of Clusters

Site	Central Referral Facility Deliveries	Peripheral Facility Deliveries	Home Deliveries[α]	Proportion of Caesarean Sections	Distance to nearest tertiary facility	Capacity for blood transfusion[Ω]	Adult Intensive Care Unit beds[Φ]	MgSO4 availability[Ω]	Total Doctors in maternity[Ω]	Clinical Officers working in maternity[Ω]	Other HCP working in maternity[Ω]	Distance from peripheral facilities to nearest tertiary facility
	Average per month: Mean (SE)	Average per month: Mean (SE)	Average per month: Mean (SE)	Average % (SD)	Average (km) (SD)	mean % of facilities	n per 1,000 deliveries	mean % of facilities	mean/1000 deliveries	mean/1000 deliveries	mean/1000 deliveries	Mean (km) (SD)
Addis Ababa	1114 (144)	657 (132)	-	22% (3)	4.3 (2.7)	15.8%	7.4	87.4%	31.2	104.1	154.1	4.3 (2.7)
Cap Haitien	682 (211)	0 (0)	63 (32)	20% (3)	14.2(5.4)	25%	0	25.0%	99.4	13.2	73.1	14.2(5.4)
Freetown	704 (148)	403 (114)	84 (28)	14% (3)	7.5 (3.7)	7.7%	0	100.0%	28.9	15.8	329.6	7.5 (3.7)
Gokak	952 (129)	188 (25)	4 (2)	31% (2)	74 (16.9)	25%	24.5	41.4%	84.4	1.2	209.9	74 (16.9)
Harare	1026 (64)	785 (53)	108 (21)	22% (25)	16.3(9.6)	12.0%	4.7	100.0%	54.8	1	246.5	16.3 (9.6)
Kampala	2223 (290)	4168 (393)	-	22% (3)	3.3 (1.3)	38.5%	2.7	61.5%	20	2.2	129.6	8.7 (4.3)
Lusaka	2231 (457)	3507 (582)	436 (60)	9% (1)	8.7 (4.3)	14.1%	3.3	79.8%	21.4	25	78.6	3.3 (1.3)
Mbale	1442 (152)	1583 (90)	-	12% (2)	19.6 (12·4)	31.7%	0	78.6%	24.1	39.4	116.6	19.6 (12.4)
Ndola	500 (38)	797 (55)	46 (10)	10% (1)	11.3 (5.1)	6.5%	4.5	77.4%	23.1	17.7	126.9	11.3 (5.1)

Zomba	2705 (394)	318 (147)	86 (21)	14% (2)	68.3 (35.2)	75%	5·3	95.4%	5	36.9	95.9	68.3 (35.2)
All sites	**1358 (766)**	**1241 (1392)**	**118[1] (137)**	**17% (11)**	**22.75 (19.36)**	**25.1%**	**10.9**	**74.7%**	**39.2**	**25.6**	**154.1**	**22.75 (19.36)**

[α] For the seven clusters that were able to systematically record home deliveries

[Φ] Intensive care unit is defined as a separate ward or room offering higher level care than the main ward.

[Ω] Recorded at trial start and a minimum of three times during trial period and average presented.

In addition to the mechanisms previously described (better availability of equipment, ease of use and confidence of all cadres of HCP to measure vital signs), the increase in equipment and training meant it was no longer acceptable to not measure vital signs on every woman. Staff reported increased motivation and interest in vital signs measurements. Only one site (Mbale) reported this in a negative light, since measurement of BP on all women increased workload. The other sites reported a reduced workload as time taken to find equipment, measure vital signs and interpret results was reduced and this task could be undertaken by a wider number of HCP.

It was frequently reported that the intervention prompted HCP to do more investigations, more quickly. This was reported to be because the traffic light display alerted users to results outside the normal range, and HCP had more confidence in the results so were better able to make decisions. This finding was not dependent on the number or skill level of staff. A minority of participants opposed this view, stating that the management was unchanged, as vital signs were always measured and acted upon. This was most commonly reported by senior HCP working in better resourced environments. Even in this setting, benefit was still reported from the traffic light alert in aiding communication between HCP.

The majority of sites also reported that the alerts were easily understood by women and untrained staff such as ambulance drivers. This was beneficial in conveying the need for management or referral, especially in sites where this was reported to be a key barrier to care (Gokak, Ndola, Zomba, Harare). Some sites reported that increased awareness of vital signs in the community resulted in increasing demand for measurements to be done (Table 16).

The impact on referrals differed between sites. Overall, 3.7% (n=2784/74,828) of women seen in peripheral maternity facilities were referred to higher level care in the control period compared to 4.4% (n=3212/73,371) in the intervention period (OR 0.89; 0.39-2.05) (data for nine sites that were able to collect denominator). However, the majority of sites demonstrated a small but significant reduction in referrals with a single site (Gokak) demonstrating a 16-fold increase (Figure 28 and Table 18). Qualitative findings suggest the increase in Gokak was a result of increased community monitoring, increased confidence in peripheral HCP to detect abnormal vital signs and convince women to attend, alongside rigorous adherence to referral protocols from rural health posts (subcentre) to primary care centres, meaning all women with asymptomatic anaemia triggering a yellow light were referred. This is in combination with an effective ambulance system, and further systems in place to cope when ambulance services were delayed, to transfer patients from primary care clinic to hospital when acute complications were detected. Therefore, the wide geographical distance (mean 74km from peripheral clinic to tertiary hospital) of this site did not impede delivery of care.

Figure 28 Forest plot of change in referral rates in individual clusters for a four-week period immediately prior to and three months after implementation. Data for nine sites that were able to collect denominator data.

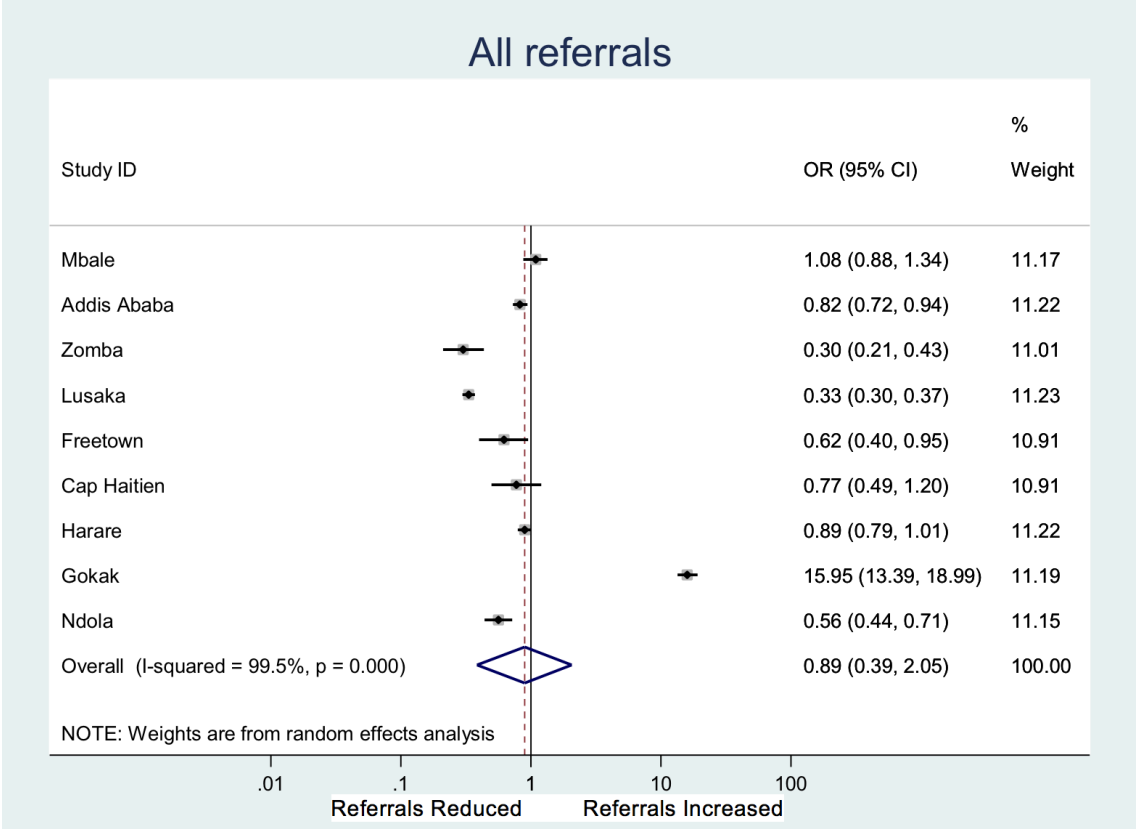


Table 18 Effect of the intervention on referrals in individual sites.

Site	**Proportion of women referred to higher level care pre-intervention$^{\Psi}$**	**Proportion of women referred to higher level care post-intervention$^{\Psi}$**	**Unadjusted Comparison**
	N (% of women seen)	N (% of women seen)	Odds Ratio (95% CI)
Freetown	45 (1.79%)	37 (1.11%)	0.62 (0.40-0.95)
Kampala	302 (*)	173 (*)	-
Ndola	158 (2.74%)	123 (2.13%)	0.56 (0.44-0.71)
Lusaka	1122 (8.3%)	471 (2.9%)	0.33 (0.30-0.37)
Gokak	144 (1.12%)	1306 (15.3%)	15.95 (13.39 – 18.99)
Cap Haitien	42 (18.19%)	54 (14.6%)	0.77 (0.49-1.20)
Mbale	159 (1.46%)	186 (1.58%)	1.08 (0.88-1.34)
Addis Ababa	532 (7.59%)	423 (6.34%)	0.82 (0.72-0.94)
Zomba	61 (1.64%)	57 (0.50%)	0.30 (0.21-0.43)
Harare	521 (8.31%)	555 (7.48%)	0.89 (0.79-1.01)
All Sites	**2784 (3.7%)**	**3212 (4.4%)**	**0.89 (0.39-2.05)**

***** Unable to collect denominator data of all women presenting to maternity care.

$^{\Psi}$ Recorded for a one-month period immediately prior to implementation, and a one-month period three months after implementation.

In contrast, Haiti reported no change in the number of referrals but that abnormal vital signs were detected and referred faster by using the traffic light alerts to convince women to attend, where cultural acceptability and perceived quality of hospital care was a barrier. However, despite the relatively small cluster size (mean 14km from peripheral clinic to tertiary hospital), the qualitative data indicated that the lack of ambulance service or funds (personal or within the health care facility) to pay for transport led to long delays contributing to morbidity and mortality, irrespective of the capacity to monitor and escalate care peripherally.

Differing acceptability of referrals and the relationship between peripheral and tertiary facilities arose as important contextual themes that may have facilitated or impeded action from the intervention. For example, HCP in Lusaka (significant benefit of the intervention) described an existing mechanism for constructive feedback on referrals between facilities, which was aided by the introduction of uniform monitoring equipment. In comparison, HCP from both peripheral and tertiary facilities in Zomba (no benefit of intervention) described negative concerns about referral, such as a lack of system to alert the recipient hospital of the pending transfer resulting in patients being refused admission. HCP in peripheral facilities in Mbale (no benefit of intervention) reported that referrals were reduced following the intervention, since pre-eclampsia could now be managed in the community, which was encouraged by the tertiary facility.

4.5 Discussion

This paper describes the mixed-methods evaluation of implementation alongside a pragmatic, stepped-wedge RCT in ten low and middle-income sites. We have demonstrated that the CRADLE intervention was delivered appropriately. All clusters demonstrated improved availability of vital signs equipment after the intervention, with

increased vital signs measurements in both our quantitative and qualitative analysis. Acceptability of the intervention was good as shown by the high proportion of facilities using the device at six and 12 months after implementation and triangulated with the qualitative findings. Referral rates were reduced in the majority of clusters which correlated with qualitative findings. Overall, we have shown no correlation between process measures within domains and no correlation between individual domains and the primary outcome.

Implementation fidelity varied between sites. As this was a pragmatic trial, it was prospectively decided that whilst fidelity would be measured, it would not be used to address and change implementation problems during the trial. This was to ensure generalisability of trial findings in future scale-up which would likely have limited capacity for detailed monitoring and feedback. The balance between delivering an intervention with high fidelity and adapting to context is widely recognised.(Moore et al., 2015) We adhered to specific components of training to ensure that delivery was similar across eight countries. However, we demonstrated that it was possible to adapt the delivery model of training whilst maintaining a high proportion of training (as described above for Gokak, India where the research team led all training).

Examples of studies that explain selection of implementation measures and analyse them alongside primary outcomes are scarce, especially in low-resource settings within the confines of limited infrastructure, research capacity and funds. This paper demonstrates that evaluation of simple implementation process measures alongside a large-scale pragmatic trial is feasible and useful in describing the quality and quantity of implementation in different sites, as well as exploring the potential mechanisms of impact. This methodology provides valuable learning for future research in LMIC by providing information to inform implementation strategies and scale-up.

Research in other fields (e.g. school education) has demonstrated that higher implementation fidelity is associated with better program outcomes.(Durlak and DuPre, 2008) We have not shown any correlation with the primary outcome. This trial was powered for the primary composite outcome, not the process outcomes. Therefore, it is possible there was insufficient power to detect a significant relationship, as suggested by the wide confidence intervals. It is also possible that this is due to the validity of the process measures themselves or their combination within domains. In the example of reach, women that do not attend health services, and were not exposed to the intervention, were not recorded. Instead a surrogate measure of change of equipment availability was selected. It could be argued that clusters with better resources were most likely to demonstrate benefit due to their capacity to respond. Alternatively, those with poor baseline resources may benefit most from the increase in equipment availability. Measuring exactly how an intervention may exert its effect in different settings is challenging within a pragmatic trial of this size. In addition, to minimise the burden of data collection only a few of the many potentially relevant domains could be assessed, and some single items were used to measure some domains. Future research should explore the relationship between implementation strength and trial outcomes and approaches to integration of data.

A further possible reason is the validity of the primary outcome measure in individual sites. As this is a stepped-wedge RCT the analysis of individual sites' data is subject to external factors and temporal trends. Whilst these were adjusted for, the variation between and within sites was greater than anticipated and seasonal trends were evident which could not be adjusted for. Due to the scale and setting of the trial, other outcomes such as diagnosis of pre-eclampsia or sepsis were not collected. Despite this, the validity of the CRADLE VSA as an accurate, robust, useful tool is maintained. Mixed-method follow up of use of the device at six months to one year after implementation is a strength of this study and supports the sustainability of the intervention. In addition, the proportion

of devices that were broken or missing was lower than our sites report for previous existing equipment. Adoption was greater in sites that had higher proportions of HCP trained or more active CRADLE champions or local research teams to support the device. This suggests that these would be important factors for future scale-up.

The strengths of this study are the predefined choice of theoretically-based, predominantly objective, quantitative measures to test hypothesised mechanisms of action. Additional strengths are the integration of qualitative and quantitative measures to triangulate findings and the pragmatic approach to data collection from many routine data sources. Funding restrictions meant the process evaluation and implementation were led by the same research team. This is a possible source of bias, although efforts were made to reduce this by undertaking, the initial framework and qualitative analysis prior to analysis of the primary outcome. Whilst the diverse settings of this trial are a strength, the number of sites, resource constraints, and the simultaneous delivery alongside a stepped wedge trial design (with strict intervals for implementation) meant that there was limited capacity to collect additional data in response to early findings.

The success of the intervention is dependent on HCP capacity to change clinical management, particularly in response to an abnormal result. The physical and geopolitical environment within which the intervention is delivered is therefore key. A recent systematic review identified that just 41 RCTs undertaken in sub-Saharan Africa across all health specialities describe any element of context.(Blacklock et al., 2016) This study selected a number of quantitative measures of health system infrastructure similar to others in the field (Betrán et al., 2018, Dumont et al., 2013) and combined this with qualitative review of clinical management and referral pathways. However, these simple measures inadequately described the complexities of these multiple health systems, their clinical pathways and readiness for change.(Leslie et al., 2017, Bergström et al., 2015)

Conclusions

Evaluation of implementation and integration of results with health outcomes is recommended by the Medical Research Council,(Moore et al., 2015) yet there is insufficient guidance or example of a suitable methodology. To our knowledge, this is the first implementation process evaluation alongside an effectiveness trial that has evaluated implementation using a mixed-methods approach and integrated these with the primary outcome with the aim of understanding differences between multiple low-resource sites. We have demonstrated the successful selection of measures to describe implementation and explore mechanism of action that were feasible. However, the lack of correlation within domains and with the primary outcome suggest that future trials should consider taking further account of ability of sites to respond, particularly when considering trials of diagnostic tests rather than direct therapeutic interventions. Measurement across all sites was necessary for comparison of implementation. Future research should consider the addition of in-depth analysis in a restricted selection of sites, for example, into clinical care pathways and factors that inform decision-making and deviation from protocols, to explain the effect of complex interventions.

5 Incidence of eclampsia and related complications across ten low and middle-resource geographical regions: secondary analysis of a cluster randomised controlled trial

5.1 Abstract

Background:

In 2015, approximately 42,000 women died as a result of HDP worldwide, over 99% of which occurred in LMIC. The aim of this paper is to describe the incidence and characteristics of eclampsia and related complications from HDP across ten LMIC geographical regions in eight countries, in relation to magnesium sulfate availability.

Methods:

This is a secondary analysis of a stepped-wedge cluster randomised-controlled trial undertaken in sub-Saharan Africa, India and Haiti. This trial implemented a novel vital sign device and training package into routine maternity care with the aim of reducing a composite outcome of maternal mortality and morbidity. Institutional-level consent was obtained and all women presenting for maternity care were eligible for inclusion. Eclampsia, stroke, admission to intensive care and maternal death from HDP data were prospectively collected from routine data sources and active case finding, together with perinatal outcomes in women with these outcomes.

Results:

Between 01st April 2016 and 30th November 2017 in 536,233 deliveries there were 2692 women with eclampsia (0.5%). In total 6.9% (n=186; 3.47/10,000 deliveries) of women with eclampsia died and a further 51 died from other complications of HDP (0.95/10,000). After planned adjustments, the implementation of the CRADLE intervention was not associated with any significant change in the rates of eclampsia, stroke, maternal death or ICU admission with HDP. Nearly one in five (17.9%) women with eclampsia, stroke and HDP causing intensive care admission or maternal death, experienced a stillbirth or

neonatal death. A third of eclampsia (33.2%; n=894) occurred in women under 20 years of age, 60.0% in women aged 20-34 years (n=1616) and 6.8% (n=182) in women aged 35 or over. Rates of eclampsia varied approximately seven-fold between sites (range 19.6/10,000 in Zambia Centre 1 to 142.0/10,000 in Sierra Leone).

Over half (55.1%) of first eclamptic fits occurred in a health care facility, with the remainder in community. Place of first fit varied substantially between sites (from 5.9% in the central referral facility in Sierra Leone to 85% in Uganda Centre 2). On average, magnesium sulfate was available in 74.7% of facilities (range 25% in Haiti to 100% in Sierra Leone and Zimbabwe). There was no detectable association between magnesium sulfate availability and the rates of eclampsia in each site (p=0.12). This analysis may be influenced by the selection of predominantly urban and peri-urban settings, monthly data on availability of magnesium sulfate, and is limited by the lack of demographic data in the denominator group.

Conclusions:

The large variation in eclampsia and maternal and neonatal fatality from HDP between countries emphasizes that inequality and inequity in health care for women with HDP persists. Alongside the growing interest in improving community detection and health education, efforts to improve quality of care within health care facilities are key. Strategies to prevent eclampsia should be informed by local data.

5.2 Background

Hypertensive disorders of pregnancy cause 14% of all maternal deaths globally, approximately 42,000 each year.(World Health Organisation, 2015b, Say et al., 2014) Nearly all of these deaths occur in low-resource settings (99%), with death from HDP in HIC very rare.(Knight M, 2016) HDP encompass chronic hypertension, gestational hypertension (new hypertension without proteinuria), pre-eclampsia (new hypertension

with proteinuria or end-organ damage after 20 weeks of gestation(Tranquilli et al., 2014)) and eclampsia. The majority of morbidity and mortality is associated with pre-eclampsia and eclampsia.

It is estimated that the prevalence of pre-eclampsia globally is 4.6% (95% CI 2.7 – 8.2%).(Abalos et al., 2013) The prevalence of eclampsia globally is reported to be 0.3%.(Abalos et al., 2014a) This is based on secondary analysis of the World Health Organisation (WHO) multi-country survey, which included 875 cases of eclampsia, collected over a short duration from only secondary or tertiary hospitals.(Abalos et al., 2014a) Women under 20 years of age, with low levels of education, in their first pregnancy are all reported to be at higher risk (Abalos et al., 2014a). Reliable data reporting the prevalence of maternal deaths related to eclampsia globally are scarce. Estimates from 16 datasets reported the case fatality rate to be 8.3%.(Abalos et al., 2013) Whereas the World Health Organisation (WHO) cross-sectional study in 29 countries reported 32 maternal deaths in this group, 3.7% of women with eclampsia.(Abalos et al., 2014a) Data from individual countries suggests that prevalence and mortality risk varies depending on region and socio-economic status.(Giordano et al., 2014)

Administration of magnesium sulfate more than halves the risk of eclampsia in women with pre-eclampsia.(Duley et al., 2010) It is considered an essential drug by the World Health Organisation,(World Health Organisation, 2017b) but data on its availability in relation to incidence of eclampsia are scarce.(Abalos et al., 2013) Planned delivery after 36 weeks of gestation is effective at preventing maternal morbidity in women with pre-eclampsia.(Koopmans et al., 2009) Evidence for other interventions effective at reducing morbidity and mortality of pre-eclampsia is mixed (Ronsmans and Campbell, 2011) and research is generally undertaken in HIC where the burden of illness is small. There is a lack of understanding around modifiable risk factors and availability of life-saving interventions, both vital in reducing the high number of deaths from this treatable cause.

The aim of this paper is to describe the incidence (per pregnancy) and characteristics of eclampsia and maternal death from severe HDP across ten geographical regions in eight low and middle-resource countries. The secondary aim is to describe the effect of novel vital sign device and educational package on eclampsia and its complications.

5.3 Methods

Study design and setting

This is a secondary analysis of a pragmatic, SW-RCT of the introduction of the CRADLE intervention (described below) into routine maternity care in ten sites across Zimbabwe, Zambia, Sierra Leone, Malawi, Ethiopia, Uganda, Haiti and India over 20 months from April 2016 to November 2017. The stepped wedge design means that at the trial start all clusters commenced data collection, all clusters then crossed from control to intervention at a randomly allocated time point, at two-monthly intervals, until all had received the intervention. The intervention effect was then determined by comparing the data points after delivery of the intervention with those in the control period. Each site comprised at least one secondary or tertiary health facility that provided comprehensive emergency obstetric care with the main peripheral facilities that refer to the central hospital. All secondary or tertiary hospitals were urban or peri-urban, but the geographical regions of peripheral facilities covered a range of settings with the mean distance varying from 3.3km to 74km. Community health care providers were included where formally involved in routine maternity care provision and supported at the district level.(Nathan et al., 2018b) The intervention was delivered to all HCP working in the site facilities.

Intervention

The CRADLE intervention consisted of the CRADLE VSA, an accurate, easy to use device that measures BP and HR and calculates SI. Results are displayed on a traffic

light EWS.(Nathan et al., 2018a, Nathan et al., 2015b) The devices were delivered with a one-off interactive training session of CRADLE Champions, who then provided ongoing training and support for use of the device in their clinical area. Further details of the development of the CRADLE intervention have previously been described.(Nathan et al., 2018b, Hoffmann et al., 2014) This intervention was compared to routine maternity care using local management guidelines.

Study Outcomes

The primary outcome of the trial was a composite outcome of maternal mortality and morbidity (at least one of eclampsia, emergency hysterectomy and maternal death) per 10,000 deliveries. In spite of a reduction in the primary outcome over time, this trial was unable to demonstrate an effect of the intervention. For the purpose of the analysis reported here, all women that presented to maternity care at any gestation or up to 42 days after delivery and were diagnosed with eclampsia or stroke, or were admitted to ICU or died as a result of HDP, between 01/04/2016 and 31/11/2017 were eligible for inclusion. The denominator was all deliveries in the trial area in the same period. Eclampsia was defined as convulsions with raised BP in the absence of a known neurological cause during pregnancy or within 42 days of delivery. Other data collected included maternal age at eclamptic fit, timing of eclampsia (antenatal including day of delivery or postnatal) and the place of first eclamptic fit (community, peripheral facility or central referral facility). The number of stillbirths and neonatal deaths up to 28 days were recorded in all women that had antenatal eclampsia, and all women that had a stroke, were admitted to ICU or died as a result of HDP.

Sites were described by the number of deliveries, number of ICU beds per 1000 deliveries and the proportion of facilities (central or peripheral) where magnesium sulfate was available. Availability of magnesium sulfate was recorded on a monthly basis. Details on the quantity available daily or individual level prescriptions were not collected. Methods of data collection were discussed and optimised based on the existing

resources available in each site. All data collectors were given detailed training to ensure comparability of results. Outcomes were triangulated across multiple sources (including referral registers, ward registers, patient records, local mortality and morbidity records, active case finding) to ensure data completeness and all outcomes checked to avoid double counting.

Ethics and consent

Ethical approval was granted by the Biomedical Sciences, Dentistry, Medicine and Natural and Mathematical Sciences Research Ethics Subcommittee at King's College London (LRS-14/15-1484). This and all local ethical approvals were in place prior to the study start. Institutional-level consent on behalf of the cluster was obtained.

Statistical methods and analysis

Statistical analyses were undertaken in Stata version 13.1. The main analysis used logistic regression with generalised estimating equations and a population-averaged model, with fixed centre effects and separate fixed linear trends in each centre for changes in outcome over time.(Hussey, 2007) Results are reported ORs with 95% confidence intervals. The trial protocol stated that individual components of the primary outcome, including eclampsia, and cause of ICU admission and maternal death and place of fit would be analysed. However, there was no predefined analysis plan for this secondary analysis.(Nathan et al., 2018b) To describe the association between eclampsia and magnesium sulfate availability, eclampsia rates for each centre, time period (month) and place of eclamptic fit were calculated. Community fits were excluded from these analyses as magnesium sulfate was not available in the community. The association between magnesium sulfate availability and total eclampsia by site used linear regression with the log of eclampsia rate with robust standard errors. The association between magnesium sulfate availability and place of fit used logistic regression with robust standard errors. Adjustments were made for period (linear) and

centre (categorical) to account for trends over time. Individual patient data were collected only for known cases.

5.4 Results

In this cohort of 526,233 deliveries there were 2692 cases of eclampsia over 20 months. This gives an incidence of eclampsia of 0.5% as shown Table 19 (50.2/10,000 deliveries). In total 6.9% (n=186; 3.47/10,000 deliveries) of women with eclampsia died (sepsis (n=4), stroke (n=4), haemorrhage (n=18), HDP (n=150) and other causes (n=10)) and a further 51 women died from other complications of HDP without having had eclampsia (0.95/10,000). Eight of the 10 sites had capacity for ICU admission, although availability of beds varied between sites (Table 19). In total, 1322 women were admitted to ICU with HDP, 27.8% of these with eclampsia (n=367) and 72.2% (n=955) with other complications of HDP. After planned adjustments for clustering and time trends in each site, the implementation of the CRADLE intervention was not associated with any significant change in the rates of eclampsia, stroke, maternal death or ICU admission with HDP.

Table 19 Rates of eclampsia, maternal death and intensive care unit admission as a result of HDP and effect of CRADLE intervention on outcomes

	Overall	**Pre-intervention**	**Post-intervention**	**Unadjusted Comparison**	**Adjusted comparison**
	Rate/10,000 deliveries n/N	Rate/10,000 deliveries n/N	Rate/10,000 deliveries n/N	OR (95% CI)	OR (95% CI)
All Eclampsia	50.20 2692/536233	53.15 1314/247238	47.77 1378/288995	0.90 (0.83–0.97)	1.32 (0.86-2.00)
All Maternal Death from HDP*	4.42 237/536233	3.84 95/247238	4.91 142/288995	1.28 (0.99-1.66)	0.84 (0.47-1.51)
Maternal death with Eclampsia	3.47 186/536233	2.87 71/247238	3.98 115/288995	1.39 (1.03-1.86)	0.79 (0.31-2.02)
Maternal death without eclampsia	0.95 51/536233	0.97 24/247238	0.93 27/288995	0.96 (0.56-1.67)	1.06 (0.38-2.93)
ICU Admission from HDP*	24.65 1322/536223	26.57 657/247238	23.01 665/288995	0.87 (0.78-0.96)	0.85 (0.72-1.02)
ICU admission with eclampsia	6.8 367/536233	9.18 227/247238	4.84 140/288995	0.53 (0.43-0.65)	0.71 (0.38-1.33)
ICU admission without eclampsia	17.81 955/536233	17.39 430/247238	18.17 525/288995	1.04 (0.92-1.19)	0.92 (0.87-0.6)
Stroke	0.62 33/536233	0.85 21/247238	0.42 12/288995	0.49 (0.24-0.99)	2.08 (0.5807.55)

* All maternal death and ICU admission from HDP includes all cases resulting from HDP, including those with and without eclampsia. Both groups are then subdivided into those with eclampsia and those secondary to other complications of HDP excluding eclampsia.

Table 20 Characteristics of Sites

Site	Number of primary level care facilities:	Number of secondary level care facilities:	Number of tertiary level care facilities:	Adult Intensive Care Unit beds	MgSO4 availability	Distance from peripheral facilities to nearest tertiary facility
	n/1000 deliveries (n)	n/1000 deliveries (n)	n/1000 deliveries (n)	n per 1,000 deliveries[1]	mean % of facilities	Mean (km) (SD)
Ethiopia	9.7	0.6	0.6	7.4	87.4%	4.3 (2.7)
Haiti	11.7	1.5	4.4	0	25.0%	14.2 (5.4)
India	55.9	18.6	0	24.5	41.4%	74 (16.9)
Malawi	1.0	2.6	0.3	5.3	95.4%	68.3 (35.2)
Sierra Leone	9.4	0.9	0.9	0	100.0%	7.5 (3.7)
Uganda Centre 2	13.6	0.3	0	3.3	79.8%	8.7 (4.3)
Uganda Centre 1	1.3	0.6	0.2	0	78.6%	19.6 (12.4)
Zambia Centre 1	4.1	0.2	0.2	2.7	61.5%	3.3 (1.3)
Zambia Centre 2	22.4	0	0.8	4.5	77.4%	11.3 (5.1)
Zimbabwe	11.5	1	0.5	4.7	100.0%	16.3 (9.6)
All sites	14.1	2.6	0.8	10.9	74.7%	22.75 (19.36)

Rates of eclampsia varied between sites from 19.6 per 10,000 deliveries in Zambia Centre 1 (Lusaka) to 142.0 per 10,000 deliveries in Sierra Leone (Figure 29, Table 21). When comparing the effect of the intervention in individual sites, further consideration is required as these are non-randomised data and are vulnerable to external influences such as seasonal trends. After planned adjustment, there was a significant reduction in eclampsia in Haiti and Zambia centre 1, a significant increase in Malawi and Uganda Centre 2 and no significant changes in other sites (Table 21). The rates of maternal death from eclampsia in each site largely reflected the incidence of eclampsia (from 0.4 per 10,000 in Zambia Centre 1 to 15.5 per 10,000 deliveries in Sierra Leone; Table 22). The range of case fatality for women with eclampsia was between 2.1% (5/242) in Zambia Centre 1 to 14.4% (18/125) in Haiti. Only 33 women in the cohort of 526,233 women were diagnosed with a stroke. ICU admission from HDP and stroke also varied between sites as shown in Figure 30 on page 209 (Table 22).

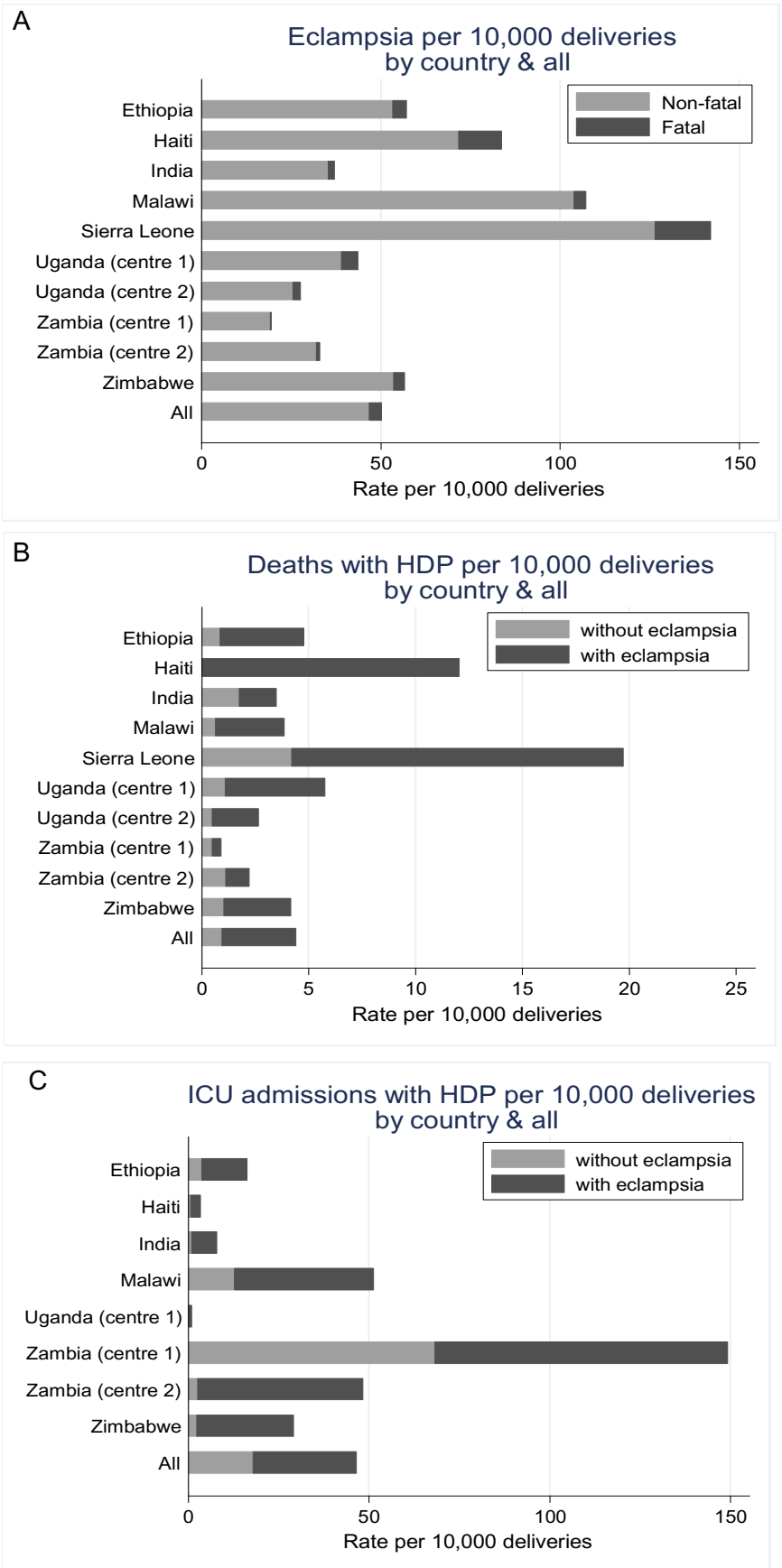


Figure 29 Rates of eclampsia (Panel A), maternal death (Panel B) and ICU admission (Panel C) from hypertensive disorders of pregnancy by site.

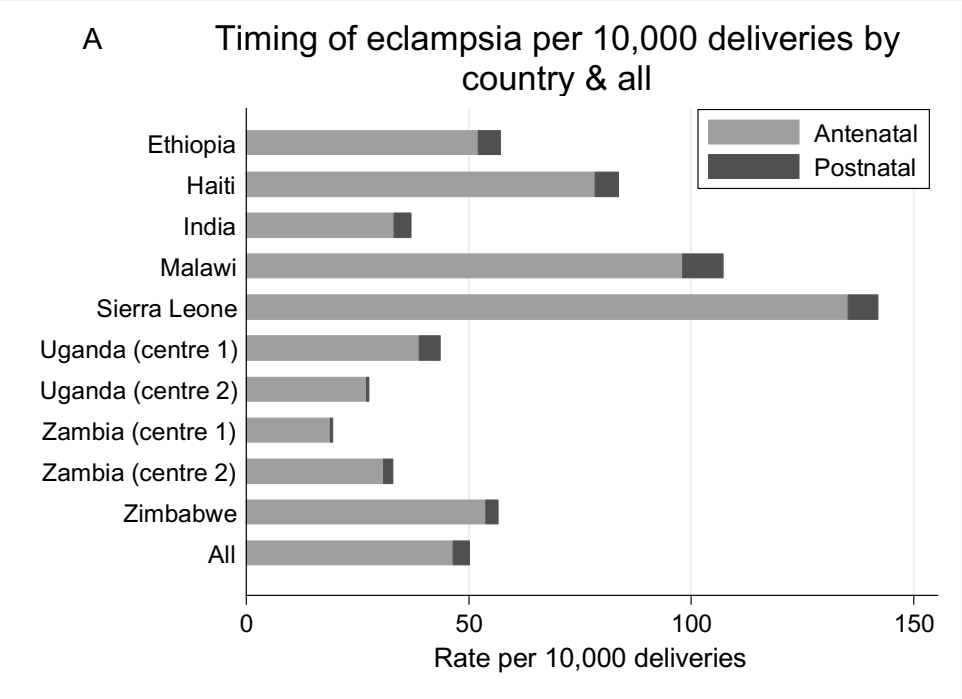
Table 21 Eclampsia by site and by intervention

Site		**Eclampsia**[1]				
		Overall	Pre-intervention	Post-intervention	Unadjusted Comparison	Adjusted Comparison
Ethiopia	Rate per 10,000 deliveries (n/N)	57.3 203/35429	55.4 135/24390	61.6 68/11039	1.11 (0.83-1.49)	1.02 (0.62-1.68)
Haiti	Rate per 10,000 deliveries (n/N)	83.8 125/14910	70.4 54/7670	98.1 71/7240	1.40 (0.98-1.99)	0.45 (0.22-0.92)
India	Rate per 10,000 deliveries (n/N)	37.2 85/22876	52 60/11531	22 25/11345	0.42 (0.26-0.67)	0.57 (0.23-1.39)
Malawi	Rate per 10,000 deliveries (n/N)	107.1 666/62165	93.3 450/48243	155 216/13922	1.67 (1.42-1.97)	2.38 (1.83-3.10)
Sierra Leone	Rate per 10,000 deliveries (n/N)	142.0 338/23,806	228 48/2106	134 290/21700	0.58 (0.43-0.79)	0.89 (0.62-1.29)
Uganda Centre 2	Rate per 10,000 deliveries (n/N)	27.6 167/60502	27.3 101/37003	28.1 66/23499	1.02 (0.76-1.40)	3.5 (1.81-6.73)
Uganda Centre 1	Rate per 10,000 deliveries (n/N)	43.7 559/127817	37.8 94/24886	45.2 465/102931	1.19 (0.96-1.49)	1.29 (0.96-1.73)
Zambia Centre 1	Rate per 10,000 deliveries (n/N)	19.6 242/123504	29.0 140/48252	13.6 102/75224	0.47 (0.36-0.60)	0.52 (0.31-0.88)
Zambia Centre 2	Rate per 10,000 deliveries (n/N)	33.1 89/26869	38.4 32/8343	30.8 57/18526	0.80 (0.52-1.24)	1.05 (0.50-2.22)
Zimbabwe	Rate per 10,000 deliveries (n/N)	56.8 218/38383	57.4 200/34814	50.4 18/3569	0.88 (0.54-1.42)	1.18 (0.67-2.08)
All sites	**Rate per 10,000 deliveries (n/N)**	**50.2 2692/536233**	**53.1 1314/247238**	**47.7 1378/288995**	**0.90 (0.83–0.97)**	**1.30 (0.82-2.05)**

Table 22 Maternal death and ICU admission with HDP and stroke by site

Site		**Maternal Death with HDP**			**ICU admission with HDP**			**Stroke**
		Total	With eclampsia	Without eclampsia	**Total**	Eclampsia (% Cases; n/N)	Other HDP	
Ethiopia	Rate per 10,000 deliveries (n/N) % Cases (n/N)	4.8 (17/35429)	4.0 (14/35429) 6.9% (14/203)	0.8 (3/35429)	11.3 (40/35429)	7.6 (27/35429) 13.3% (27/203)	3.7 (13/35429)	0.6 (2/35429)
Haiti	Rate per 10,000 deliveries (n/N) % Cases (n/N)	12.1 (18/14910)	12.1 (18/14910) 14.4% (18/125)	0.0 (0/14910)	12.1 (18/14910)	8.1 (12/14910) 9.6% (12/125)	0.67 (1/14910)	3.4 (5/14910)
India	Rate per 10,000 deliveries (n/N) % Cases (n/N)	3.5 (8/22876)	1.7 (4/22876) 4.7% (4/85)	1.7 (4/22876)	3.5 (8/22876)	2.6 (6/22876) 7.1% (6/85)	0.9 (2/22876)	1.7 (4/22876)
Malawi	Rate per 10,000 deliveries (n/N) % Cases (n/N)	3.9 (24/62165)	3.2 (20/62165) 3.0% (20/666)	0.6 (4/62165)	18.3 (114/62165)	5.6 (35/62165) 5.3% (35/666)	12.7 (79/62165)	0 (0/62165)
Sierra Leone	Rate per 10,000 deliveries (n/N) % Cases (n/N)	19.7 (47/23806)	15.5 (37/23806) 10.9% (37/338)	4.2 (10/23806)	0.0 (0/23806)	0.0 (0/23806) 0.0% (0/338)	0 (0/23806)	1.3 (3/23806)
Uganda Centre 1	Rate per 10,000 deliveries (n/N) % Cases (n/N)	5.8 (74/127817)	4.7 (60/127817) 10.7% (60/559)	1.1 (14/127817)	0.5 (6/127817)	0.4 (5/127817) 0.9% (5/559)	0.1 (1/127817)	0.8 (10/127817)

Uganda Centre 2	Rate per 10,000 deliveries (n/N) % Cases (n/N)	2.6 (16/60502)	2.1 (13/60502) 7.8% (13/167)	0.5 (3/60502)	0 (0/60502)	0 (0/60502) 0% (0/167)	0 (0/60502)	0 (0/60502)
Zambia Centre 1	Rate per 10,000 deliveries (n/N) % Cases (n/N)	0.9 (11/123504)	0.4 (5/123504) 2.1% (5/242)	0.5 (6/123504)	87.9 (1085/123504)	19.6 (242/123504) 100% (242/242)	68.3 (843/123504)	0.4 (5/123504)
Zambia Centre 2	Rate per 10,000 deliveries (n/N) % Cases (n/N)	2.2 (6/26869)	1.1 (3/26869) 3.4% (3/89)	1.1 (3/26869)	8.9 (24/26869)	6.3 (17/26869) 19% (17/89)	2.6 (7/26869)	0.4 (1/26869)
Zimbabwe	Rate per 10,000 deliveries (n/N) % Cases (n/N)	4.2 (16/38383)	3.1 (12/38383) 5.5% (12/218)	1.0 (4/38383)	8.3 (32/38383)	6.0 (23/38383) 10.6% (23/218)	2.3 (9/38383)	0.8 (3/38383)
All sites	**Rate per10,000 deliveries (n/N) % Cases (n/N)**	**4.4 (237/536233)**	**3.5 (186/536233) 6.9%(186/2692)**	**1.0(51/536233)**	**24.7 (1322/536223)**	**6.8 (367/536233) 13.6% (367/2792)**	**17.8 (955/536233)**	**0.6 (33/536233)**



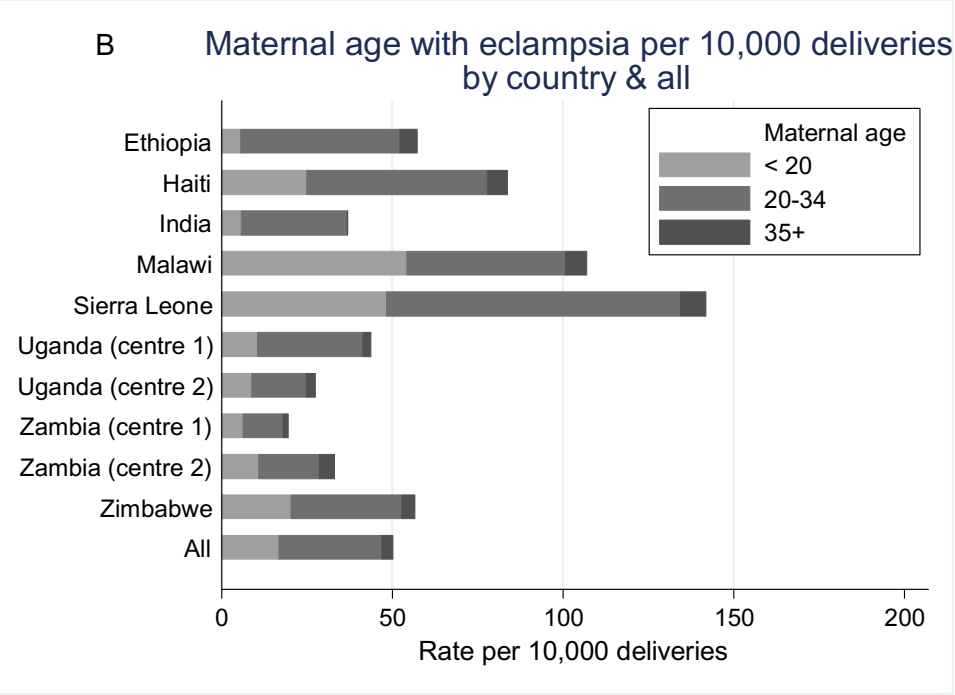


Figure 30 Characteristics of eclampsia by timing (Panel A) and maternal age (Panel B) by siteCorresponding numbers are given in Table 23

Table 23 Characteristics of eclampsia by site

Site		Antenatal Eclampsia[1]	Postnatal Eclampsia	Age <20	Age 20-34	Age 35 or over
Ethiopia	Rate per 10,000 deliveries (n/N)	52.2 (185/35429)	5.1 (18/35429)	5.6 (20/35429)	46.6 (165/35429)	5.1 (18/35429)
	% Cases (n/N)	91.1% (185/203)	8.9% (18/203)	9.9% (20/203)	81.3% (165/203)	8.9% (18/203)
Haiti	Rate per 10,000 deliveries (n/N)	78.5 (117/14910)	5.4 (8/14910)	24.8 (37/14910)	53.0 (79/14910)	6.0 (9/14910)
	% Cases (n/N)	93.6% (117/125)	6.4% (8/125)	29.6% (37/125)	63.2% (79/125)	7.2% (9/125)
India	Rate per 10,000 deliveries (n/N)	33.2 (76/22876)	3.9 (9/22876)	5.7 (13/22876)	31.0 (71/22876)	0.4 (1/22876)
	% Cases (n/N)	89.4% (76/85)	10.6% (9/85)	15.3% (13/85)	83.5% (71/85)	1.2% (1/85)
Malawi	Rate per 10,000 deliveries (n/N)	98.1 (610/62165)	9.0 (56/62165)	54.2 (337/62165)	46.5 (289/62165)	6.4 (40/62165)
	% Cases (n/N)	91.6% (610/666)	8.4% (56/666)	50.1% (337/666)	43.4% (289/666)	6.0% (40/666)
Sierra Leone	Rate per 10,000 deliveries (n/N)	135.2 (322/23806)	6.7 (16/23806)	48.3 (115/23806)	86.1 (205/23806)	7.6 (18/23806)
	% Cases (n/N)	95.3% (322/338)	4.7% (16/338)	34.0% (115/338)	60.1% (205/338)	5.3% (18/338)
Uganda Centre 1	Rate per 10,000 deliveries (n/N)	38.9 (497/127817)	4.9 (62/127817)	10.6 (135/127817)	30.8 (394/127817)	2.3 (30/127817)
	% Cases (n/N)	88.9% (497/559)	11.1% (62/559)	24.2% (135/559)	70.5% (394/559)	5.4% (30/559)

Uganda	Rate per 10,000 deliveries (n/N)	27.1 (164/60502)	0.5 (3/60502)	8.8 (53/60502)	16.0 (97/60502)	2.8 (17/60502)
Centre 2	% Cases (n/N)	98.2% (164/167)	1.8% (3/167)	31.7% (53/167)	58.1% (97/167)	10.2% (17/167)
Zambia	Rate per 10,000 deliveries (n/N)	18.9 (234/123504)	0.6 (8/123504)	6.2 (77/123504)	11.7 (144/123504)	1.7 (21/123504)
Centre 1	% Cases (n/N)	96.7% (234/242)	3.3% (8/242)	31.8% (77/242)	59.5% (144/242)	8.7% (21/242)
Zambia	Rate per 10,000 deliveries (n/N)	30.9 (83/26869)	22.3 (6/26869)	10.8 (29/26869)	17.9 (48/26869)	4.5 (12/26869)
Centre 2	% Cases (n/N)	93.3% (83/89)	6.7% (6/89)	32.6% (29/89)	53.9% (48/89)	13.5% (12/89)
Zimbabwe	Rate per 10,000 deliveries (n/N)	53.9 (207/38383)	2.9 (11/38383)	20.3 (78/38383)	32.3 (124/38383)	4.2 (16/38383)
	% Cases (n/N)	95.0% (207/218)	5.0% (11/218)	35.8% (78/218)	56.9% (124/218)	7.3% (16/218)
All sites	**Rate per 10,000 deliveries (n/N)**	**46.5 (2495/536233)**	**3.7 (197/536233)**	**16.7 (894/536233)**	**30.1 (1616/536233)**	**3.4 (182/536233)**
	% Cases (n/N)	**92.7% (2495/2692)**	**7.3% (197/2692)**	**33.2% (894/2692)**	**60.0% (1616/2692)**	**6.8% (182/2692)**

[1.] Includes eclampsia on day of delivery

Across all sites, 92.7% (n=2495) of eclampsia occurred in the antenatal period and 7.3% (n=197) in the postnatal period. This was similar between sites (range 88.9% in Uganda Centre 1 to 98.2% in Uganda Centre 2) (Figure 30; Table 23). Approximately a third of eclampsia (33.2%; n=894) occurred in women aged under 20 years. These proportions varied between sites from 10% in Ethiopia to 51% in Malawi (Figure 30; Table 23). The majority of eclampsia occurred in women aged 20-34 years of age (60.0%; n=1616); 6.8% (n=182) occurred in women aged 35 or over.

In total there were 10 central referral facilities and 268 peripheral facilities. Nearly half of all first eclamptic fits occurred in the community (44.9%; range 30.8% in Malawi to 66.0% in Freetown, Table 24) with 31.2% occurring for the first time in central referral facilities (range 5.9% in Sierra Leone to 85.0% in Uganda Centre 2) and 23.9% in peripheral facilities (range 4.7% in India to 33.0% in Ethiopia). On average magnesium sulfate was available in 74.7% of facilities (range 25% in Haiti to 100% in Sierra Leone and Zimbabwe). Availability of magnesium sulfate did not significantly change during the trial period. There was no significant association between the overall availability of magnesium sulfate in central and peripheral referral facilities and the proportion of eclampsia that occurred in each (p=0.42; Table 24). There was also no detectable association between the proportion of facilities with magnesium sulfate available and the rates of eclampsia in each country (p=0.12). Of the 1210 women that had their first eclamptic fit in the community 7.5% (91/1210) died; of the 1482 that their first fit in a facility, 6.4% (95/1482) died.

Table 24 Place of fit and proportion of facilities with Magnesium Sulfate available on average over trial duration

Site	**Total**	**Central Referral Facility**	**Peripheral Facility**	**Community**	**Magnesium sulfate availability**
	n	N (% of eclampsia)	N (% of eclampsia)	N (% of eclampsia)	Mean availability over trial duration (%)
Ethiopia	203	57 (28.1%)	67 (33.0%)	79 (38.9%)	87.4%
Haiti	125	52 (41.6%)	16 (12.8%)	57 (45.6%)	25.0%
India	85	27(31.8%)	4 (4.7%)	54 (63.5%)	95.4%
Malawi	666	242 (36.3%)	219 (32.9%)	205 (30.8%)	100.0%
Sierra Leone	338	20 (5.9%)	95 (28.1%)	223 (66.0%)	41.4%
Uganda Centre 1	559	161 (28.8%)	125 (22.4%)	273 (48.8%)	61.5%
Uganda Centre 2	167	142 (85%)	17 (10.2%)	8 (4.8%)	78.6%
Zambia Centre 1	242	34 (14.0%)	61 (25.2%)	147 (60.7%)	79.8%
Zambia Centre 2	89	38 (42.7%)	13 (14.6%)	38 (42.7%)	77.4%
Zimbabwe	218	66 (30.3%)	26 (11.9%)	126 (57.8%)	100.0%
All sites	**2692**	**839 (31.2%)**	**643 (23.9%)**	**1210 (44.9%)**	**74.7%**

In this group of 3493 women with antenatal eclampsia (n=2495), stroke and HDP causing ICU admission or maternal death (n=998), rates of stillbirth and neonatal mortality were very high (17.9%; n=625). The rates of stillbirth and neonatal mortality were higher following severe HDP (resulting in stroke, ICU admission or maternal death)without eclampsia than in women with eclampsia (stillbirth and neonatal death 22.8% (n=228) in women with HDP without eclampsia and 15.9% (n=397) in women with eclampsia; Table 25). Overall rates of stillbirth and neonatal mortality in women with eclampsia varied between sites from 4.1% in Malawi to 23.1% in Uganda Centre 1 (Table 26).

Table 25 Perinatal outcomes for mothers with antenatal eclampsia or HDP causing death or ICU admission*

Perinatal outcomes	**Overall n/N (%)**
All stillbirth and neonatal death in women with HDP	625/3493 (17.9%)
All stillbirth and neonatal death in women with antenatal eclampsia	397/2495 (15.9%)
Pregnancies ending in stillbirth	322/2495 (12.9%)
Neonatal death	75/2495 (3.0%)
All stillbirth and neonatal death in women with HDP causing ICU admission or death without eclampsia	228/998 (22.8%)
Pregnancies ending in stillbirth	197/998 (19.7%)
Neonatal death	31/998 (3.1%)

*Excludes 12 with missing delivery information and 45 that went home after eclampsia without delivery and were not followed up.

Table 26 Perinatal outcomes for mothers with antenatal eclampsia or HDP causing death or ICU admission* by site

Sites		**All HDP**	**HDP with Antenatal eclampsia**			**HDP causing ICU admission or maternal death without eclampsia**		
		All stillbirth and neonatal death in women with HDP	**All still births and neonatal deaths**	**Pregnancies with Stillbirth**	**Pregnancies Neonatal Death[1]**	**All still births and neonatal deaths**	**Pregnancies with Stillbirth**	**Pregnancies with Neonatal Death[1]**
Ethiopia	n/N (%)	42/100 (42%)	36/85 (19.4%)	32/185 (17.3%)	4/185 (2.2%)	6/15 (40.0%)	6/15 (40.0%)	0/15 (0%)
Haiti	n/N (%)	17/118 (14.4%)	17/117 (14.5%)	17/117 (14.5%)	0/117 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Sierra Leone	n/N (%)	78/334 (37.8%)	72/322 (22.4%	59/322 (18.3%)	13/322 (40.3%)	6/12 (50%)	5/12 (41.7%)	1/12 (8.3%)
India	n/N (%)	13/81 (16.0%)	10/76 (13.2%)	3/76 (3.9%)	7/76 (9.2%)	3/5 (60%)	2/5 (40.0%)	1/5 (20.0%)
Malawi	n/N (%)	35/691 (5.1%)	25/610 (41.0%)	20/610 (3.3%)	5/610 (0.8%)	10/81 (12.3%)	9/81 (11.1%)	1/81 (1.2%)
Uganda Centre 1	n/N (%)	122/514 (23.7%)	115/497 (23.1%)	91/497 (18.3%)	24/497 (4.8%)	7/17 (41.2%)	6/17 (35.3%)	1/17 (5.9%)

Uganda Centre 2	n/N (%)	16/167 (9.6%)	14/164 (8.5%)	14/164 (8.5%)	0/164 (0%)	2/3 (66.7%)	2/3 (66.7%)	0/3 (0%)
Zambia Centre 1	n/N (%)	237/1077 (22.0%)	50/234 (21.4%)	44/234 (18.8%)	6/234 (2.6%)	187/843 (22.2%)	162 / 843 (19.2%)	25/846 (3.0%)
Zambia Centre 2	n/N (%)	15/93 (16.1%)	11/83 (13.3%)	7/83 (8.4%)	4/83 (4.8%)	4/10 (40%)	3/10 (33.3%)	1/10 (10.0%)
Zimbabwe	n/N (%)	50/218 (22.9%)	47/207 (22.7%)	35/207 (16.9%)	12/207 (58.0%)	3/11 (27.3%)	2/11 (18.2%)	1/11 (9.1%)
All sites	**n/N (%)**	**625/3493 (17.9%)**	**397/2495 (15.9%)**	**322/2495 (12.9%)**	**75/2495 (3.0%)**	**228/998 (22.8%)**	**197/998 (19.7%)**	**31/998 (3.1%)**

*Excludes 12 with missing delivery information and 45 that went home after eclampsia without delivery and were not followed up

5.5 Discussion

Overall, we have reported that 0.5% of women in our sites experienced eclampsia, 57.2% of women with eclampsia are admitted to ICU and 6.9% die. Our individual site analysis has shown large variation both in the rates of eclampsia but also the rates of maternal death and ICU admission from HDP. Stroke was a rare outcome in all our sites. The majority of eclampsia across all sites first occurs in the community (44.9%), in the antenatal period (92.6%) and in women aged 20-34 (60.0%). Overall, the implementation of the CRADLE intervention was not associated with any significant change in the rates of eclampsia, stroke, maternal death or ICU admission with HDP but the effect in individual sites varied.

To our knowledge, this is the largest prospectively collected dataset of women with eclampsia. The strengths of these data are the rigorous method of prospective data collection, verified from multiple sources and inclusion of multiple countries and settings. The majority of existing data has focused on eclampsia presenting to secondary or tertiary hospitals.(Abalos et al., 2014a) The data presented here improve the accuracy of incidence estimates by including cases across the health system, including from primary health care facilities and community cases.

Although the geographical settings varied, it is a limitation of this study that the majority of sites were urban or peri-urban. These were selected as a substantial proportion of births occur here. This, in addition to the inclusion of the national referral hospital in many of our sites, means the incidence of complications from HDP may be higher than country wide levels. Due to the size of the study it was not feasible to collect demographic data in the denominator group, therefore the proportion of eclampsia in different age groups and perinatal outcomes cannot be presented at the population level. Comparisons by intervention on perinatal outcomes or age or place of eclampsia are therefore not

presented. The effect of the intervention in individual sites needs further consideration as this is non-randomised analyses. The number of eclampsia and HDP were based on the data reported by attending clinicians in the selected hospitals; it was not feasible to undertake additional searching in all sites to identify cases not reported; however, the inclusion of only maternal death and ICU admission from HDP mean that mis-diagnosis is less likely. The availability of ICU beds varied between sites, therefore admission to ICU was dependent on capacity, above severity of HDP.

A systematic review of the global incidence of HDP, including 129 studies, found that just 22% of studies reported magnesium sulfate use.(Abalos et al., 2013) Therefore, collection of this data on a monthly basis, at the level of the facility, is a strength of this study. However, as daily fluctuations in the quantity available, or the number of doses prescribed remains unknown, it is possible that supply may not have been adequate to meet demand. Furthermore, 44.9% of eclampsia occurred for the first time in the community, therefore were not included in this analysis. In practice, women may have attended health care facilities (with or without magnesium sulfate available) prior to eclampsia in the community, therefore it is a limitation of the study that individual case details could not be obtained.

In the post MDG era the focus of global health is on not just reducing mortality but also reducing morbidity.(United Nations General Assembly, 2015) Yet in this study, the large variation in fatality from eclampsia between countries emphasizes that both inequality and inequity in management of HDP persists. It has been previously reported that organ dysfunction is up to 60 times more frequent in women with eclampsia compared to women without eclampsia.(Abalos et al., 2014a) Therefore, the very high rates of maternal death in some countries compared to previously reported estimates,(Abalos et al., 2014a, Giordano et al., 2014) highlight that the true burden of disease in these countries may be even greater than previously recognised and HDP should remain firmly on the global agenda.

This study has shown no effect of the CRADLE intervention on complications of HDP. It is possible that the intervention increased detection but without the capacity to improve management. The primary purpose of the study was to collect accurate data, and therefore detailed case information on clinical management was not routinely collected, given the resource constraints of the trial. It is challenging to therefore draw conclusions on differences in management that may also have contributed to variations in the rate of eclampsia and resulting morbidity seen. However, it is evident that Zambia Centre 1 (Lusaka) had the lowest rate of eclampsia and case fatality and admitted substantially more patients to ICU than any other site. This was possible as they have a specialist unit specifically for women with HDP that provides continuous monitoring and close observation by trained staff. In comparison, the site in Freetown in Sierra Leone that had the highest rate of eclampsia and case fatality has no higher-level care available. The availability of monitoring to rapidly detect deteriorations and initiate treatment such as antihypertensives, magnesium sulfate and timely delivery, are likely to be important. This is in keeping with reports that the largest reductions in maternal mortality from HDP in England and Wales were achieved with improved surveillance diagnosis and timely delivery, with further benefit from fluid-restriction management protocols and increased use of anticonvulsant therapies in more recent decades.(Shennan et al., 2017)

In this study, nearly a third of eclampsia occurred in women aged under 20 years. This varied greatly between sites, with Malawi reporting that half of eclampsia cases occurred in women aged under 20 years. Other studies have reported rates of 26%(Abalos et al., 2014a) to 55%.(Vigil-De Gracia, 2015) Whilst, this study did not collect demographic data in all deliveries, nationwide demographic data shows that 15% of births in Malawi in 2015 to 2016 occurred in women aged under 20 years.(National Statistical Office [Malawi] and ICF) Existing literature suggests that teenage pregnant women are at greater risk of eclampsia(Ganchimeg et al., 2014) and their care should be prioritized in clinical

practice. Interventions aiming to overcome the complex socio-cultural needs of this group to improve access to health care and prevent eclampsia warrant further research.

This study also presents novel data on the place of fit, previously only reported in smaller cohort studies, where 74.5% (n=142) were reported to occur before hospital admission in Latin America.(Vigil-De Gracia, 2015) Our data demonstrate that over half of women experience their first fit in a health care facility, despite the relatively good availability of magnesium sulfate in these settings. However, the proportion of eclampsia that first occurred in health care facilities compared to the community varied substantially between sites. This suggests that the most appropriate interventions and strategies to reduce eclampsia should be informed by local incidence data. For example, in centres in Sierra Leone, Zambia Centre 1 and India, where a high proportion of eclampsia occurs in the community, interventions aiming to improve community monitoring and overcome barriers to accessing care including health education(Khowaja et al., 2016) may be the most appropriate use of resources. In contrast, in sites in Uganda (Centre 2) and Haiti, targeting the quality of care within facilities may be a more effective strategy in preventing eclampsia. Therefore, when vital actions such as treatment of severe hypertension with magnesium sulfate to prevent eclampsia (Duley et al., 2010) and timely delivery of the baby (Koopmans et al., 2009) are recommended, national and international policy makers may also recommend collection of regional data to identify how these interventions should be delivered to achieve the greatest benefit locally, thus maximizing their impact and identifying the most appropriate use of resources.

In conclusion, this analysis provides accurate contemporaneous estimates of incidence of eclampsia and severe HDP from the largest known prospective dataset across eight low and middle-resource settings. These data highlight that mortality (for the woman and baby) from eclampsia remains high and higher-risk groups exist that should be prioritized in research and policy. Use of magnesium sulfate to prevent eclampsia and timely delivery after diagnosis remain important strategies to reduce maternal and perinatal

mortality from HDP at the facility level but interventions should also be targeted to meet the need of the region.

6 Discussion

The research findings of this thesis have been discussed within the four papers presented in Chapters 2 to 5. This chapter therefore explores overriding findings across the studies against the objectives of this thesis, explores the implications of the studies and overall strengths and limitations of the thesis. These are used to identify unanswered questions and recommendations for future research.

6.1 Synthesis of principal findings

Chapter 2 presents findings from the first objective of this thesis, to determine the acceptability of the CRADLE intervention and the feasibility of its implementation and evaluation. This was determined by a mixed-methods study. The high proportion of HCP trained within a short time frame suggested that the methods of implementation were feasible. The fast uptake into routine maternity care after training, and positive responses from HCP that the CRADLE intervention was used daily in preference to existing equipment suggested the intervention was acceptable. Several barriers to uptake and use were identified and these were used to refine the training package and implementation strategies. In addition, the assumptions of the intervention and its potential mechanisms of action were identified and used to select process measures to evaluate within the trial. Nine of the ten main trial sites achieved ethical approval for the feasibility study and optimised the methods of data collection for the primary composite outcome. The data collected was used to prospectively modify the components of the

composite outcome, refine the power calculation and inform the randomisation sequence. The protocol for the main trial was refined.

The second objective of this thesis was to test the efficacy of the CRADLE intervention in reducing maternal morbidity and mortality in low resource settings. Chapter 3 describes the results of the 20-month SW-RCT, during which there were 536,223 deliveries and the primary outcome occurred in 4067 women. Whilst there was a decrease in the number of women that experienced a primary outcome after the intervention (79.4/10,000 deliveries to 72.8/10,000 post-intervention; OR 0.92; 95% CI 0.86–0.97), after planned adjustments for differences in the event rate between and within clusters over time, this could not be attributed to the intervention (adjusted OR 1.22; 95% CI 0.73–2.06; p=0.45). The effect of the intervention varied between clusters. After planned adjustments, significant benefit was shown in Freetown, Cap Haitien and Lusaka but an increase in the event rate was shown in Mbale, Mulago and Zomba.

The third objective was to evaluate the implementation of the CRADLE intervention in order to understand the trial results; this is described in Chapter 4. The intervention was implemented with reasonable fidelity (61.1% of maternity staff trained). The intervention improved the availability of working vital signs equipment in all sites. This was likely due to the limited resource availability prior to the trial and high acceptability of the intervention shown in the feasibility phase. Uptake was high and sustained beyond implementation (73.1% and 73.5% of clinical areas using solely the VSA at six months and 12 months respectively). In both the quantitative and qualitative data, the intervention improved quality of care (97.6% of women attending maternity care having their vital signs measured compared to 79.2% prior to the intervention; OR 1.30; 95% CI 1.29-1.31). Overall, implementation was of adequate quality and quantity to have supported any finding on the effect of the intervention, had the main trial demonstrated one. The implementation measures for individual sites were also used in an attempt to explain the differences in the effect of the intervention between sites. There was wide

variation in each of the measures of implementation within and between sites. Whether tested alone or as a composite score the measures of implementation could not explain the differences in the effectiveness of the intervention between sites.

The final objective of this thesis was to explore the incidence of eclampsia and morbidity from HDP which is described in Chapter 5. As the largest cohort of women with eclampsia to date, this component of the thesis confirmed incidence data from the literature, demonstrating that 0.5% of women (n=2692/536223) developed eclampsia with a case fatality of 6.9% (n=186/2692). In addition, the study identified new data on place of first eclamptic fit in different countries (5.9% of first fits occurred in the central referral facility in Sierra Leone vs. 85% in Mbale, Uganda).

6.2 Strengths and weaknesses of this study in comparison to the literature

The individual strengths and limitations of each paper have been discussed in Chapters 2 to 5. This section aims to provide an overview of the strengths and limitations of the studies as a whole in the context of existing literature.

Intervention

It is a strength of this study that the components of the intervention were tested and refined in a feasibility phase. This is in keeping with examples from the literature that mixed-methods formative development of complex interventions in maternal health in LMIC are beneficial.(Bartlett et al., 2016, Morrison et al., 2008, Boyd and Windsor, 2003, Modi et al., 2015, Mazumder et al., 2018) This likely contributed to the high acceptability of the intervention. The intervention itself was also rigorously evaluated for accuracy and ease of use (Nathan et al., 2015a, Nathan et al., 2015b, Nathan et al., 2018a, Nathan et

al., 2017) and the educational package was interactive and multi-faceted, the best for behavioural change,(Althabe et al., 2008) although, knowledge gained from training was not evaluated in the main trial. A further limitation is that the level of ongoing support provided by the implementation team and the CRADLE champions differed between sites. This variation may have contributed to the differences in the effect of the intervention between sites, but as this component of the intervention was not measured its contribution is unknown.

There is growing evidence to suggest that task-sharing with CHWs is an important strategy in improving maternal mortality and morbidity, as described in Section 1.4.4. It is a strength of this study that it utilised CHWs in clusters where they were routinely involved in maternity care, thus adding a further potential mechanism of action by improving community detection and access to health services. However, it is a limitation that this was only possible in two of the ten sites and there was no mechanism to determine the specific impact of this component. Informal task-sharing was also found to be prevalent with many different groups of individuals frequently supporting routine vital signs measurement such as psychosocial counsellors in Zambia, volunteers in Malawi and Sierra Leone and nursing students. Given the pragmatic nature of the study and ease of use of the intervention these groups were trained alongside usual HCP. However, they were not counted in the numbers trained or staffing availability, and therefore again their contribution to the intervention was unmeasured. This could have been a potential reason for the differences of the effect of the intervention between sites. Further research should explore the impact of formal task sharing with CHWs to improve early detection of pregnancy complications using the CRADLE VSA.

Trial Design

The robust trial design is a strength compared to other evaluations of complex interventions in this setting, that frequently utilise observational or quasi-experimental designs that are greater risk of bias and cannot demonstrate causality. Indeed, a

systematic review of non-pharmacological interventions aiming to reduce maternal morbidity in sub-Saharan Africa reported that just one third of the 73 studies included between 2000 to 2015 were RCTs.(Wekesah et al., 2016)

A major limitation was the impact that the multi-country design had on statistical power. The feasibility study demonstrated large variation in the event rate between countries. This was used to inform the randomisation sequence (balancing clusters with similar event rates). In addition, the assumptions used in the power calculation allowed for some anticipated variation. However, the actual level of variation was much greater than expected and month-to-month variation in the event rate in each cluster was also large. This was not anticipated from the pilot data as the duration was only three months long with only six clusters collecting a full three months of data, during which variation was expected while sites refined the methods of data collection. Furthermore, in a SW-RCT it is vital to adjust for temporal trends as explained in Section 1.5.2. As this was a multi-country study these trends were presumed to be different in each site, but this could not be factored into the power calculation due to lack of reliable data for eclampsia and hysterectomy. All of this in combination meant that despite having more outcomes than anticipated (n=4067 compared to n=2450 required for 95% power using stated assumptions) the trial was insufficiently powered to demonstrate an effect of the intervention. As this is the first SW-RCT undertaken across multiple LMIC, these results are novel and of particular importance to others planning similar trial designs. The data from this trial could be used to inform the statistical assumptions for all future research aiming to reduce these important clinical outcomes in LMIC. Further analysis is required to ensure these can be presented and disseminated so that future research can benefit.

Seasonal effects were also demonstrated in several sites, especially Malawi. A systematic review identified six studies exploring seasonality and HDP in LMIC, five of which demonstrated an association.(TePoel et al., 2011) However, the number of cases was small and the majority of these studies were more than 20 years old. Further

research is required to explore these seasonal effects and determine whether they correlate with potential environmental factors such as availability of food, access to facilities or rates of malaria.

Selection of outcomes and potential bias

Even though the research team collecting data were not masked to the intervention, the choice of unequivocal, objective outcomes means there was a low risk of measurement bias. This is a strength compared to other studies, where only 29% of studies evaluating non-pharmacological interventions to improve maternal morbidity in sub-Saharan Africa included a specific maternal outcome (Wekesah et al., 2016) and a further review identified just four trials that included maternal mortality as an outcome.(Campbell and Graham, 2006) It could be argued that a primary process outcome such as timely management of pregnancy complications would have been logical and feasible endpoint for this study. However, robust, accurate measures of quality of care are challenging in low-resource settings as they are frequently dependent on completion of checklists, review of patient charts or observation of practice, which are all associated with methodological issues.(Pirkle et al., 2011, Dettrick et al., 2013) In addition, surrogate outcomes do not always correlate with health outcomes (Rothwell, 2005) and they are less likely to directly translate into policy changes. Therefore, the robust clinical end point is a major strength of this study in comparison to others.

Other factors that have reduced bias in this study were the decision not to disclose the randomisation sequence to clusters until after they were enrolled, therefore reducing the risk of selection bias in the clusters. In addition, the roll out throughout the health system and eligibility of all women attending maternity care not only meant that the results would have had high external validity, but the risk of recruitment bias was low. Local primary investigators in each site identified the main facilities that referred to the secondary or tertiary hospital and invited them to participate in the trial, representing the majority of facilities within a geographical area. Systematic invitation to all facilities within the area

could have further reduced selection bias and increased the external validity of the trial results. However, the intervention was only delivered to the facilities where data collection was undertaken, and this remained the same pre- and post-intervention; it is therefore unlikely to have impacted the effectiveness of the intervention. It is also possible that women may have presented at the tertiary hospital from facilities outside of those included in the trial. This means they would not have been exposed to the intervention before referral. Systematically recording changes to the physical and political environment in each trial site monthly, meant that the impact of this unknown was reduced, as it could be assumed that the proportion of women attending from external facilities remained roughly the same in the control and intervention periods. Further secondary analysis could be undertaken, restricted to women referred from facilities included in the trial area, to determine whether this contributed to differences in the effect of the intervention between sites.

Data collection

Section 1.2.2 described the challenges of data collection and trends in maternal mortality worldwide. The estimated MMR identified in the study countries were lower than that described in 2015 by the WHO.(World Health Organisation, 2015b) This may be because the geographical regions included in the study were all urban or peri-urban which are associated with lower mortality and may not reflect country wide rates. In addition, the inclusion of the national tertiary referral hospital in most clusters, with relatively small geographical distances for referral in most sites, may reflect better access to high quality care and an increased likelihood of having a skilled attendant at delivery compared to national levels. Finally, this may represent the method of data collection. Previous estimates of maternal mortality are based on diverse sources including household surveys and verbal autopsies, these can be inaccurate as they are subject to recall, however they systematically count deaths in the community. It is a strength of this study that maternal mortality was collected from routine hospital sources, in addition to active case finding, and that this occurred across the health system, but there was no

systematic method of community data collection and so community deaths may be underreported.

Despite the lower MMR in comparison to the literature, the proportion of deaths caused by haemorrhage, sepsis, hypertension and other causes are comparable to existing literature, as described in Section 1.2.3.(Say et al., 2014) In this trial, cause of death was identified from patient documents and where necessary individual case details verified with relevant HCP. This was feasible as we had a specific team of data collectors, whereas global figures are estimated based on vital registration data, government reports, and verbal autopsies. HCP and women could not be masked to the intervention. Data collectors visited facilities regularly to collect outcome data. It is therefore plausible that the mechanism of data collection was associated with informal audit and feedback which may have indirectly improved the care provided by HCP over time, which would bias the results in favour of the intervention. However, all data collectors had extensive training and were advised against this to minimise this risk.

Interpretation of implementation outcomes

The addition of an integrated, concurrent mixed-method process evaluation, that included objective, quantitative measures of fidelity, dose, reach and adoption is also a strength and is unique in this field and setting. This study utilised several measures of local context to describe existing resources in addition to exploring potential mechanisms of the intervention such as referral processes. This is a strength compared to other literature. A recent systematic review identified that just 41 RCTs undertaken in sub-Saharan Africa across all health specialities describe any element of context.(Blacklock et al., 2016) However, the simple measures of resource and staff numbers, chosen in this trial and others undertaken LMIC,(Betrán et al., 2018, Dumont et al., 2013) inadequately described the complexities of access to high-quality healthcare.

As this study is of a diagnostic test not a treatment, its success was dependent on reaching the right population, at the right time and triggering a pathway of action. In addition, in this study these may have differed in each local context. Therefore, failure to fully understand each of these steps means the dramatic benefit shown in some sites compared to others cannot be explained. Future research should consider in depth review of the clinical pathways and actual patient care in addition to the cultural, political and organisational environment in a subset of sites where the intervention was shown to be effective compared to where it may have caused harm. This may highlight differences in more detailed factors that may have contributed to the different results between sites, for example: behavioural factors such as the acceptability of referral pathways, quality of care factors such as the extent to which women actually receive effective interventions (e.g. magnesium sulfate to prevent eclampsia), and physical factors such as delays whilst awaiting transport for referral.

This trial followed many of the MRC recommendations for evaluation of complex interventions. Triangulating data from multiple sources has given more strength to conclusions (e.g. the high proportion of clinical areas using the VSA at six months correlates with the lack of previous equipment and ease of use). However, in a study of this size, undertaken in resource poor environments with constraints of infrastructure, and limited funding, every outcome measured was a balance of the level of information it provided over the burden of collection. Therefore, even with this approach, the understanding of how the intervention impacts on clinical practice in order to change health outcomes, as well as the sustainability of the intervention, was not fully determined. The WHO has tested a survey method of reviewing facilities including laboratory tests, intrapartum care facilities and human resources.(Shah et al., 2008) Others have suggested mixed-methods to allow for evaluation of organisational and political changes in response to an intervention.(Hawe et al., 2004) Since this study utilised all available guidance and reflects a uniquely comprehensive evaluation in this field, it also highlights that more evidence is required in order to guide researchers in

selection of process measures that are feasible to collect in LMIC but also the most important for understanding intervention effects.

6.3 Meaning of the study: implications for clinicians or policymakers and future research

The aim of the study was to explore the acceptability and feasibility of the CRADLE intervention then evaluate its efficacy at reducing maternal mortality and morbidity. The acceptability and feasibility of the intervention has been demonstrated by both quantitative and qualitative measures in the feasibility study and main trial. This adds to the literature that mixed-method feasibility studies are beneficial in intervention development and testing trial processes. Future research should aim to ensure this formative period is of a suitable duration for data collection methods to stabilise and any subsequent trends or monthly variation in the data identified prior to the main trial.

Overall, despite the rigorous trial design that was well suited to evaluate the intervention in this setting, effectiveness of the intervention at reducing mortality and morbidity has not been shown due to methodological challenges. The intervention effect differed in individual sites. This was a planned secondary analysis, but individual site analysis was not by conventional randomised group. It is more vulnerable to external influences such as policy changes or strike action and month-to-month variation especially in clusters that had a short time with or without the intervention. As a result, there is insufficient evidence on which to recommend the intervention directly for incorporation into policy in any cluster region or internationally. Future research evaluating the effectiveness of this intervention could consider a cluster or SW-RCT with the district as the level of randomisation within a single country. In depth analysis of clinical care pathways in a sub-set of districts by more detailed resource availability surveys, direct observation of and measuring a number of intermediate process measures, such as the proportion of

women with HDP that receive magnesium sulfate and the proportion with PPH that receive uterotonics may be recommended, whilst maintaining unequivocal health outcomes as the primary end-point. This thesis also contains the largest cohort of women with eclampsia to date and provides novel information on where eclampsia is occurring, which differs between countries. This indicates that the mechanism by which interventions to prevent eclampsia are delivered, could be targeted to specific needs of the region. Future research of the VSA to improve detection of hypertension and monitoring in the community may be most appropriate in some regions, whereas use of monitoring within the hospital alongside packages of care such as timely delivery of the baby may be more appropriate in other regions (additional funding has been achieved for this, Appendix 0).

Future SW-RCT across multiple countries for other interventions aiming to reduce maternal mortality and morbidity should ideally be suitably powered to demonstrate an effect of the intervention in each country. This will require substantial pilot data so that temporal trends in each country and accurate estimates of variation between sites can be used to ensure the trial is adequately powered.

This thesis has demonstrated that measuring implementation alongside effectiveness is feasible and beneficial in describing differences between clusters in maternal health in LIC. Further research is required to determine how to select process measures and measures of context that are both important and practical and how these can be integrated with outcome measures to understand differences between multiple sites.

References

AARVOLD, A. B. R., RYAN, H. M., MAGEE, L. A., VON DADELSZEN, P., FJELL, C. & WALLEY, K. R. 2017. Multiple Organ Dysfunction Score Is Superior to the Obstetric-Specific Sepsis in Obstetrics Score in Predicting Mortality in Septic Obstetric Patients. *Critical Care Medicine,* 45**,** e49-e57.

ABALOS, E., CHAMILLARD, M., DIAZ, V., TUNCALP, Ö. & GÜLMEZOGLU, A. M. 2016. Antenatal care for healthy pregnant women: a mapping of interventions from existing guidelines to inform the development of new WHO guidance on antenatal care. *Bjog,* 123**,** 519-528.

ABALOS, E., CUESTA, C., CARROLI, G., QURESHI, Z., WIDMER, M., VOGEL, J. P. & SOUZA, J. P. 2014a. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG: An International Journal of Obstetrics & Gynaecology,* 121**,** 14-24.

ABALOS, E., CUESTA, C., GROSSO, A. L., CHOU, D. & SAY, L. 2013. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics & Gynecology and Reproductive Biology,* 170**,** 1-7.

ABALOS, E., DULEY, L. & STEYN, D. W. 2014b. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews*.

ABDU, M., WILSON, A., MHANGO, C., TAKI, F., COOMARASAMY, A. & LISSAUER, D. 2017. Resource availability for the management of maternal sepsis in Malawi, other low-income countries, and lower-middle-income countries. *International Journal of Gynecology & Obstetrics,* 140**,** 175-183.

ACOSTA, C. D., BHATTACHARYA, S., TUFFNELL, D., KURINCZUK, J. J. & KNIGHT, M. 2012. Maternal sepsis: a Scottish population-based case-control study. *Bjog,* 119**,** 474-83.

ACOSTA, C. D. & KNIGHT, M. 2013. Sepsis and maternal mortality. *Curr Opin Obstet Gynecol,* 25**,** 109-16.

ACOSTA, C. D., KNIGHT, M., LEE, H. C., KURINCZUK, J. J., GOULD, J. B. & LYNDON, A. 2013. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. *PLoS One,* 8**,** e67175.

ACOSTA, C. D., KURINCZUK, J. J., LUCAS, D. N., TUFFNELL, D. J., SELLERS, S., KNIGHT, M. & ON BEHALF OF THE UNITED KINGDOM OBSTETRIC SURVEILLANCE, S. 2014. Severe Maternal Sepsis in the UK, 2011–2012: A National Case-Control Study. *PLoS Medicine,* 11**,** e1001672.

ADAM, T., LIM, S. S., MEHTA, S., BHUTTA, Z. A., FOGSTAD, H., MATHAI, M., ZUPAN, J. & DARMSTADT, G. L. 2005. Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. *Bmj,* 331**,** 1107.

ADEGOKE, A. A., CAMPBELL, M., OGUNDEJI, M. O., LAWOYIN, T. & THOMSON, A. M. 2013. Place of birth or place of death: An evaluation of 1139 maternal deaths in Nigeria. *Midwifery,* 29**,** e115-e121.

AKEJU, D. O., VIDLER, M., SOTUNSA, J. O., OSIBERU, M. O., ORENUGA, E. O., OLADAPO, O. T., ADEPOJU, A. A., QURESHI, R., SAWCHUCK, D., ADETORO, O. O., VON DADELSZEN, P., DADA, O. A. & THE, C. N. F. W. G. 2016. Human resource constraints and the prospect of task-sharing among community health workers for the detection of early signs of pre-eclampsia in Ogun State, Nigeria. *Reproductive Health,* 13**,** 111.

AL-RUBAIE, Z. T. A., ASKIE, L. M., RAY, J. G., HUDSON, H. M. & LORD, S. J. 2016. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology,* 123**,** 1441-1452.

ALBRIGHT, C. M., ALI, T. N., LOPES, V., ROUSE, D. J. & ANDERSON, B. L. 2014. The Sepsis in Obstetrics Score: a model to identify risk of morbidity from sepsis in pregnancy. *American Journal of Obstetrics and Gynecology,* 211**,** 39.e1-39.e8.

ALLGOWER, M. & BURRI, C. 1967. ["Shock index"]. *Dtsch Med Wochenschr,* 92**,** 1947-50.

ALTHABE, F., BERGEL, E., CAFFERATA, M. L., GIBBONS, L., CIAPPONI, A. & ALEMAN, A. 2008. Strategies for improving the quality of health care in maternal and child health in low- and middle-income countries: an overview of systematic reviews. *Paediatr Perinat Epidemiol,* 22.

ANAND, S. & BÄRNIGHAUSEN, T. 2004. Human resources and health outcomes: cross-country econometric study. *The Lancet,* 364**,** 1603-1609.

ANDERSON, U. D., OLSSON, M. G., KRISTENSEN, K. H., AKERSTROM, B. & HANSSON, S. R. 2012. Review: Biochemical markers to predict preeclampsia. *Placenta,* 33 Suppl**,** S42-7.

AUSTIN, D. M., SADLER, L., MCLINTOCK, C., MCARTHUR, C., MASSON, V., FARQUHAR, C. & RHODES, S. 2014. Early detection of severe maternal morbidity: a retrospective assessment of the role of an Early Warning Score System. *Aust N Z J Obstet Gynaecol,* 54**,** 152-5.

BAKER, E. C., HEZELGRAVE, N., MAGESA, S. M., EDMONDS, S., DE GREEFF, A. & SHENNAN, A. 2012. Introduction of automated blood pressure devices intended for a low resource setting in rural Tanzania. *Trop Doct,* 42**,** 101-3.

BANDA, R., FYLKESNES, K. & SANDØY, I. F. 2015. Rural-urban differentials in pregnancy-related mortality in Zambia: estimates using data collected in a census. *Population Health Metrics,* 13**,** 32.

BARTLETT, L. A., LEFEVRE, A. E., MIR, F., SOOFI, S., ARIF, S., MITRA, D. K., QUAIYUM, M. A., SHAKOOR, S., ISLAM, M. S., CONNOR, N. E., WINCH, P. J., RELLER, M. E., SHAH, R., EL ARIFEEN, S., BAQUI, A. H., BHUTTA, Z. A., ZAIDI, A., SAHA, S., AHMED, S. A. & ON BEHALF OF THE, A.-P. S. S. G. 2016. The development and evaluation of a community-based clinical diagnosis tool and treatment regimen for postpartum sepsis in Bangladesh and Pakistan. *Reproductive Health,* 13**,** 16.

BARTSCH, E., MEDCALF, K. E., PARK, A. L. & RAY, J. G. 2016. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *Bmj,* 353**,** i1753.

BASCH, C. E., SLIEPCEVICH, E. M., GOLD, R. S., DUNCAN, D. F. & KOLBE, L. J. 1985. Avoiding type III errors in health education program evaluations: a case study. *Health Educ Q,* 12**,** 315-31.

BAUER, M. E., BAUER, S. T., RAJALA, B., MACEACHERN, M. P., POLLEY, L. S., CHILDERS, D. & ARONOFF, D. M. 2014. Maternal physiologic parameters in relationship to systemic inflammatory response syndrome criteria: a systematic review and meta-analysis. *Obstet Gynecol,* 124**,** 535-41.

BELLO, N. A., WOOLLEY, J. J., CLEARY, K. L., FALZON, L., ALPERT, B. S., OPARIL, S., CUTTER, G., WAPNER, R., MUNTNER, P., TITA, A. T. & SHIMBO, D. 2018. Accuracy of Blood Pressure Measurement Devices in Pregnancy: A Systematic Review of Validation Studies. *Hypertension,* 71**,** 326-335.

BERGER, T., GREEN, J., HORECZKO, T., HAGAR, Y., GARG, N., SUAREZ, A., PANACEK, E. & SHAPIRO, N. 2013. Shock Index and Early Recognition of Sepsis in the Emergency Department: Pilot Study. *Western Journal of Emergency Medicine,* 14**,** 168-174.

BERGH, A.-M., KERBER, K., ABWAO, S., DE-GRAFT JOHNSON, J., ALIGANYIRA, P., DAVY, K., GAMACHE, N., KANTE, M., LIGOWE, R., LUHANGA, R., MUKARUGWIRO, B., NGABO, F., RAWLINS, B., SAYINZOGA, F., SENGENDO, N. H., SYLLA, M., TAYLOR, R., VAN ROOYEN, E. & ZOUNGRANA, J. 2014. Implementing facility-based kangaroo mother care services: lessons from a multi-country study in Africa. *BMC Health Services Research,* 14**,** 293.

BERGH, A. M., ARSALO, I., MALAN, A. F., PATRICK, M., PATTINSON, R. C. & PHILLIPS, N. 2005. Measuring implementation progress in kangaroo mother care. *Acta Paediatr,* 94.

BERGH, A. M., BALOYI, S. & PATTINSON, R. C. 2015. What is the impact of multi-professional emergency obstetric and neonatal care training? *Best Pract Res Clin Obstet Gynaecol,* 29**,** 1028-43.

BERGSTRÖM, A., SKEEN, S., DUC, D. M., BLANDON, E. Z., ESTABROOKS, C., GUSTAVSSON, P., HOA, D. T. P., KÄLLESTÅL, C., MÅLQVIST, M., NGA, N. T., PERSSON, L.-Å., PERVIN, J., PETERSON, S., RAHMAN, A., SELLING, K., SQUIRES, J. E., TOMLINSON, M., WAISWA, P. & WALLIN, L. 2015. Health system context and implementation of evidence-based practices—development and validation of the Context Assessment for Community Health (COACH) tool for low- and middle-income settings. *Implementation Science,* 10**,** 120.

BETRÁN, A. P., BERGEL, E., GRIFFIN, S., MELO, A., NGUYEN, M. H., CARBONELL, A., MONDLANE, S., MERIALDI, M., TEMMERMAN, M., GÜLMEZOGLU, A. M., ALEMAN, A., ALTHABE, F., BIZA, A., CRAHAY, B., CHAVANE, L., COLOMAR, M., DELVAUX, T., DIQUE ALI, U., FERSURELA, L., GEELHOED, D., JILLE-TAAS, I., MALAPENDE, C. R., LANGA, C., OSMAN, N. B., REQUEJO, J. & TIMBE, G. 2018. Provision of medical supply kits to improve quality of antenatal care in Mozambique: a stepped-wedge cluster randomised trial. *The Lancet Global Health,* 6**,** e57-e65.

BICK, D. E., SANDALL, J., FURUTA, M., WEE, M. Y., ISAACS, R., SMITH, G. B. & BEAKE, S. 2014. A national cross sectional survey of heads of midwifery services of uptake, benefits and barriers to use of obstetric early warning systems (EWS) by midwives. *Midwifery,* 30**,** 1140-6.

BIRKHAHN, R. H., GAETA, T. J., BEI, R. & BOVE, J. J. 2002. Shock index in the first trimester of pregnancy and its relationship to ruptured ectopic pregnancy. *Acad Emerg Med,* 9**,** 115-9.

BIRKHAHN, R. H., GAETA, T. J., VAN DEUSEN, S. K. & TLOCZKOWSKI, J. 2003. The ability of traditional vital signs and shock index to identify ruptured ectopic pregnancy. *Am J Obstet Gynecol,* 189**,** 1293-6.

BLACKLOCK, C., GONÇALVES BRADLEY, D. C., MICKAN, S., WILLCOX, M., ROBERTS, N., BERGSTRÖM, A. & MANT, D. 2016. Impact of Contextual Factors on the Effect of Interventions to Improve Health Worker Performance in Sub-Saharan Africa: Review of Randomised Clinical Trials. *PLoS ONE,* 11**,** e0145206.

BLANC, A. K., WINFREY, W. & ROSS, J. 2013. New findings for maternal mortality age patterns: aggregated results for 38 countries. *PLoS One,* 8**,** e59864.

BOENE, H., VIDLER, M., AUGUSTO, O., SIDAT, M., MACETE, E., MENENDEZ, C., SAWCHUCK, D., QURESHI, R., VON DADELSZEN, P., MUNGUAMBE, K. & SEVENE, E. 2016. Community health worker knowledge and management of pre-eclampsia in southern Mozambique. *Reprod Health,* 13**,** 105.

BONE, R. C., BALK, R. A., CERRA, F. B., DELLINGER, R. P., FEIN, A. M., KNAUS, W. A., SCHEIN, R. M. H. & SIBBALD, W. J. 1992. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. *CHEST,* 101**,** 1644-1655.

BONELL, C., FLETCHER, A., MORTON, M., LORENC, T. & MOORE, L. 2012. Realist randomised controlled trials: a new approach to evaluating complex public health interventions. *Soc Sci Med,* 75**,** 2299-306.

BONET, M., NOGUEIRA PILEGGI, V., RIJKEN, M. J., COOMARASAMY, A., LISSAUER, D., SOUZA, J. P. & GÜLMEZOGLU, A. M. 2017. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. *Reproductive Health,* 14**,** 67.

BONET, M., SOUZA, J. P., ABALOS, E., FAWOLE, B., KNIGHT, M., KOUANDA, S., LUMBIGANON, P., NABHAN, A., NADISAUSKIENE, R., BRIZUELA, V. & METIN GÜLMEZOGLU, A. 2018. The global maternal sepsis study and awareness campaign (GLOSS): study protocol. *Reproductive Health,* 15**,** 16.

BOROVAC-PINHEIRO, A., PACAGNELLA, R. C., PUZZI-FERNANDES, C. & CECATTI, J. G. 2018. Case-control study of shock index among women who did and did not receive blood transfusions due to postpartum hemorrhage. *Int J Gynaecol Obstet,* 140**,** 93-97.

BOUTRON, I., MOHER, D., ALTMAN, D. G., SCHULZ, K. F. & RAVAUD, P. 2008. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med,* 148.

BOYD, N. R. & WINDSOR, R. A. 2003. A formative evaluation in maternal and child health practice: the Partners for Life Nutrition Education Program for pregnant women. *Matern Child Health J,* 7**,** 137-43.

BRADLEY, F., WILES, R., KINMONTH, A. L., MANT, D. & GANTLEY, M. 1999. Development and evaluation of complex interventions in health services research: case study of the Southampton heart integrated care project (SHIP). The SHIP Collaborative Group. *Bmj,* 318**,** 711-5.

BROUGHON PIPKIN, F. 2007. *Dewhurst's textbook of obstetrics & gynaecology,* Malden, Mass., Malden, Mass. : Blackwell Pub.

BROWN, C. A. & LILFORD, R. J. 2006. The stepped wedge trial design: a systematic review. *BMC Med Res Methodol,* 6**,** 54.

BROWN, M. A., MAGEE, L. A., KENNY, L. C., KARUMANCHI, S. A., MCCARTHY, F. P., SAITO, S., HALL, D. R., WARREN, C. E., ADOYI, G. & ISHAKU, S. 2018. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*.

BRUNELLI, V. B. & PREFUMO, F. 2015. Quality of first trimester risk prediction models for pre-eclampsia: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology,* 122**,** 904-914.

BUA, J., PAINA, L. & KIRACHO, E. E. 2015. Lessons learnt during the process of setup and implementation of the voucher scheme in Eastern Uganda: a mixed methods study. *Implementation Science,* 10**,** 108.

CALLAGHAN, M., FORD, N. & SCHNEIDER, H. 2010. A systematic review of task- shifting for HIV treatment and care in Africa. *Hum Resour Health,* 8**,** 8.

CALVERT, C., THOMAS, S. L., RONSMANS, C., WAGNER, K. S., ADLER, A. J. & FILIPPI, V. 2012. Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. *PLoS One,* 7**,** e41114.

CAMERON, M. 2012. *Definitions, Vital Statistics and Risk Factors: an Overview,* London, Sapiens Publishing.

CAMPBELL MJ, W. S. 2012. *How to design, analyse and report cluster randomised trials in medicine and health service research*, John Wiley and Sons.

CAMPBELL, O. M. R. & GRAHAM, W. J. 2006. Strategies for reducing maternal mortality: getting on with what works. *The Lancet,* 368**,** 1284-1299.

CANNING, D., SHAH, I. H., PEARSON, E., PRADHAN, E., KARRA, M., SENDEROWICZ, L., BARNIGHAUSEN, T., SPIEGELMAN, D. & LANGER, A. 2016. Institutionalizing postpartum intrauterine device (IUD) services in Sri Lanka, Tanzania, and Nepal: study protocol for a cluster-randomized stepped-wedge trial. *BMC Pregnancy Childbirth,* 16**,** 362.

CANTWELL, R., CLUTTON-BROCK, T., COOPER, G., DAWSON, A., DRIFE, J., GARROD, D., HARPER, A., HULBERT, D., LUCAS, S., MCCLURE, J., MILLWARD-SADLER, H., NEILSON, J., NELSON-PIERCY, C., NORMAN, J., O'HERLIHY, C., OATES, M., SHAKESPEARE, J., DE SWIET, M., WILLIAMSON, C., BEALE, V., KNIGHT, M., LENNOX, C., MILLER, A., PARMAR, D., ROGERS, J. & SPRINGETT, A. 2011. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *Bjog,* 118 Suppl 1**,** 1-203.

CARLE, C., ALEXANDER, P., COLUMB, M. & JOHAL, J. 2013. Design and internal validation of an obstetric early warning score: secondary analysis of the Intensive Care National Audit and Research Centre Case Mix Programme database. *Anaesthesia,* 68**,** 354-67.

CARROLI, G., ROONEY, C. & VILLAR, J. 2001. How effective is antenatal care in preventing maternal mortality and serious morbidity? An overview of the evidence. *Paediatr Perinat Epidemiol,* 15 Suppl 1**,** 1-42.

CHAMBERLAIN, G. P., F.B 1998. *Clinical Physiology in Obstetrics*, Blackwell Science.

CHAVANE, L., MERIALDI, M., BETRÁN, A. P., REQUEJO-HARRIS, J., BERGEL, E., ALEMAN, A., COLOMAR, M., CAFFERATA, M. L., CARBONELL, A., CRAHAY, B., DELVAUX, T., GEELHOED, D., GÜLMEZOGLU, M., MALAPENDE, C. R., MELO, A., NGUYEN, M. H., OSMAN, N. B., WIDMER, M., TEMMERMAN, M. & ALTHABE, F. 2014. Implementation of evidence-based antenatal care in Mozambique: a cluster randomized controlled trial: study protocol. *BMC Health Services Research,* 14**,** 228-228.

CHEN, J., HILLMAN, K., BELLOMO, R., FLABOURIS, A., FINFER, S. & CRETIKOS, M. 2009. The impact of introducing medical emergency team system on the documentations of vital signs. *Resuscitation,* 80**,** 35-43.

CHINKHUMBA, J., DE ALLEGRI, M., MUULA, A. S. & ROBBERSTAD, B. 2014. Maternal and perinatal mortality by place of delivery in sub-Saharan Africa: a meta-analysis of population-based cohort studies. *BMC Public Health,* 14**,** 1014.

CHOWDHURY, M. E., RONSMANS, C., KILLEWO, J., ANWAR, I., GAUSIA, K., DAS-GUPTA, S., BLUM, L. S., DIELTIENS, G., MARSHALL, T., SAHA, S. & BORGHI, J. 2006. Equity in use of home-based or facility-based skilled obstetric care in rural Bangladesh: an observational study. *The Lancet,* 367**,** 327-332.

CHURCHILL, D., DULEY, L., THORNTON, J. G. & JONES, L. 2013. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. *Cochrane Database Syst Rev***,** Cd003106.

CLEARY, K. L., SIDDIQ, Z., ANANTH, C. V., WRIGHT, J. D., TOO, G., D'ALTON, M. E. & FRIEDMAN, A. M. 2018. Use of Antihypertensive Medications During Delivery Hospitalizations Complicated by Preeclampsia. *Obstet Gynecol,* 131**,** 441-450.

CNOSSEN, J. S., VOLLEBREGT, K. C., DE VRIEZE, N., TER RIET, G., MOL, B. W., FRANX, A., KHAN, K. S. & VAN DER POST, J. A. 2008. Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis. *Bmj,* 336**,** 1117-20.

COLEMAN, A. J., STEEL, S. D., ASHWORTH, M., VOWLER, S. L. & SHENNAN, A. 2005. Accuracy of the pressure scale of sphygmomanometers in clinical use within primary care. *Blood Press Monit,* 10**,** 181-8.

COLQUHOUN, H., LEEMAN, J., MICHIE, S., LOKKER, C., BRAGGE, P., HEMPEL, S., MCKIBBON, K. A., PETERS, G.-J. Y., STEVENS, K. R., WILSON, M. G. & GRIMSHAW, J. 2014. Towards a common terminology: a simplified framework of interventions to promote and integrate evidence into health practices, systems, and policies. *Implementation Science,* 9**,** 781.

CONNOLLY, F., BYRNE, D., LYDON, S., WALSH, C. & O'CONNOR, P. 2017. Barriers and facilitators related to the implementation of a physiological track and trigger system: A systematic review of the qualitative evidence. *International Journal for Quality in Health Care,* 29**,** 973-980.

CRAIG, P., DIEPPE, P., MACINTYRE, S., MICHIE, S., NAZARETH, I. & PETTICREW, M. 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ,* 337.

CURRAN, G. M., BAUER, M., MITTMAN, B., PYNE, J. M. & STETLER, C. 2012. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care,* 50**,** 217-26.

DAMIANI, E., DONATI, A., SERAFINI, G., RINALDI, L., ADRARIO, E., PELAIA, P., BUSANI, S. & GIRARDIS, M. 2015. Effect of Performance Improvement Programs on Compliance with Sepsis Bundles and Mortality: A Systematic Review and Meta-Analysis of Observational Studies. *PLOS ONE,* 10**,** e0125827.

DAMSCHRODER, L. J., ARON, D. C., KEITH, R. E., KIRSH, S. R., ALEXANDER, J. A. & LOWERY, J. C. 2009. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci,* 4**,** 50.

DARMSTADT, G. L., CHOI, Y., ARIFEEN, S. E., BARI, S., RAHMAN, S. M., MANNAN, I., SERAJI, H. R., WINCH, P. J., SAHA, S. K., AHMED, A. S. M. N. U., AHMED, S., BEGUM, N., LEE, A. C. C., BLACK, R. E., SANTOSHAM, M., CROOK, D., BAQUI, A. H. & FOR THE BANGLADESH PROJAHNMO-2 STUDY, G. 2010. Evaluation of a Cluster-Randomized Controlled Trial of a Package of Community-Based Maternal and Newborn Interventions in Mirzapur, Bangladesh. *PLoS ONE,* 5**,** e9696.

DAS, M. K., ARORA, N. K., DALPATH, S., KUMAR, S., QAZI, S. A. & BAHL, R. 2018. Improving quality of care for perinatal and newborn care at district and sub-district hospitals in Haryana, India: Implementation research protocol. *J Adv Nurs*.

DAWSON, A. J., BUCHAN, J., DUFFIELD, C., HOMER, C. S. & WIJEWARDENA, K. 2014. Task shifting and sharing in maternal and reproductive health in low-income countries: a narrative synthesis of current evidence. *Health Policy Plan,* 29**,** 396-408.

DE GREEFF, A., NATHAN, H., STAFFORD, N., LIU, B. & SHENNAN, A. H. 2008. Development of an accurate oscillometric blood pressure device for low resource settings. *Blood Press Monit.* England.

DELLER, B., TRIPATHI, V., STENDER, S., OTOLORIN, E., JOHNSON, P. & CARR, C. 2015. Task shifting in maternal and newborn health care: Key components from policy to implementation. *International Journal of Gynecology & Obstetrics,* 130**,** S25-S31.

DELLINGER, R. P., LEVY, M. M., RHODES, A., ANNANE, D., GERLACH, H., OPAL, S. M., SEVRANSKY, J. E., SPRUNG, C. L., DOUGLAS, I. S., JAESCHKE, R., OSBORN, T. M., NUNNALLY, M. E., TOWNSEND, S. R., REINHART, K., KLEINPELL, R. M., ANGUS, D. C., DEUTSCHMAN, C. S., MACHADO, F. R., RUBENFELD, G. D., WEBB, S. A., BEALE, R. J., VINCENT, J. L. & MORENO, R. 2013. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med,* 41**,** 580-637.

DERSIMONIAN, R. & LAIRD, N. 1986. Meta-analysis in clinical trials. *Control Clin Trials,* 7**,** 177-88.

DETTRICK, Z., FIRTH, S. & JIMENEZ SOTO, E. 2013. Do strategies to improve quality of maternal and child health care in lower and middle income countries lead to improved outcomes? A review of the evidence. *PLoS One,* 8**,** e83070.

DOVLO, D. 2004. Using mid-level cadres as substitutes for internationally mobile health professionals in Africa. A desk review. *Human Resources for Health,* 2**,** 7-7.

DOWSWELL, T., CARROLI, G., DULEY, L., GATES, S., GULMEZOGLU, A. M., KHAN-NEELOFUR, D. & PIAGGIO, G. 2015. Alternative versus standard packages of antenatal care for low-risk pregnancy. *Cochrane Database Syst Rev***,** Cd000934.

DUCKITT, K. & HARRINGTON, D. 2005. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ : British Medical Journal,* 330**,** 565-565.

DULEY, L. 2009. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol,* 33**,** 130-7.

DULEY, L., GÜLMEZOGLU, A. M., HENDERSON-SMART, D. J. & CHOU, D. 2010. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database of Systematic Reviews*.

DULEY, L., HENDERSON-SMART, D. J., MEHER, S. & KING, J. F. 2007. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev***,** Cd004659.

DULEY, L., MEHER, S. & JONES, L. 2013. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database of Systematic Reviews*.
DUMONT, A., FOURNIER, P., ABRAHAMOWICZ, M., TRAORE, M., HADDAD, S. & FRASER, W. D. 2013. Quality of care, risk management, and technology in obstetrics to reduce hospital-based maternal mortality in Senegal and Mali (QUARITE): a cluster-randomised trial. *Lancet,* 382.
DUONG, D. V., BINNS, C. W. & LEE, A. H. 2004. Utilization of delivery services at the primary health care level in rural Vietnam. *Soc Sci Med,* 59**,** 2585-95.
DURLAK, J. A. & DUPRE, E. P. 2008. Implementation matters: a review of research on the influence of implementation on program outcomes and the factors affecting implementation. *Am J Community Psychol,* 41.
EDWARDS, M., MCKAY, H., VAN LEUVAN, C. & MITCHELL, I. 2010. Modified Early Warning Scores: inaccurate summation or inaccurate assignment of score? *Critical Care,* 14**,** P257-P257.
EDWARDS, S. E., GROBMAN, W. A., LAPPEN, J. R., WINTER, C., FOX, R., LENGUERRAND, E. & DRAYCOTT, T. 2015. Modified obstetric early warning scoring systems (MOEWS): validating the diagnostic performance for severe sepsis in women with chorioamnionitis. *American Journal of Obstetrics and Gynecology,* 212**,** 536.e1-536.e8.
EL AYADI, A. M., NATHAN, H. L., SEED, P. T., BUTRICK, E. A., HEZELGRAVE, N. L., SHENNAN, A. H. & MILLER, S. 2016. Vital Sign Prediction of Adverse Maternal Outcomes in Women with Hypovolemic Shock: The Role of Shock Index. *PLoS One,* 11**,** e0148729.
ELDRIDGE S, K. S. 2012. *A practical guide to cluster randomised trials in health services research.* , John Wiley & Sons.
ELDRIDGE, S. M., ASHBY, D., FEDER, G. S., RUDNICKA, A. R. & UKOUMUNNE, O. C. 2004. Lessons for cluster randomized trials in the twenty-first century: a systematic review of trials in primary care. *Clinical Trials,* 1**,** 80-90.
FARRIS, R. P., WILL, J. C., KHAVJOU, O. & FINKELSTEIN, E. A. 2007. Beyond effectiveness: evaluating the public health impact of the WISEWOMAN program. *Am J Public Health,* 97**,** 641-7.
FISHBEIN, M. 2000. The role of theory in HIV prevention. *AIDS Care,* 12**,** 273-8.
FORD, I. & NORRIE, J. 2016. Pragmatic Trials. *New England Journal of Medicine,* 375**,** 454-463.
FRETHEIM, A., HÅVELSRUD, K. & OXMAN, A. D. 2006. Rational Prescribing in Primary care (RaPP): process evaluation of an intervention to improve prescribing of antihypertensive and cholesterol-lowering drugs. *Implementation Science,* 1**,** 19.
FULTON, B. D., SCHEFFLER, R. M., SPARKES, S. P., AUH, E. Y., VUJICIC, M. & SOUCAT, A. 2011. Health workforce skill mix and task shifting in low income countries: a review of recent evidence. *Human Resources for Health,* 9**,** 1-1.
GABRYSCH, S. & CAMPBELL, O. M. 2009. Still too far to walk: literature review of the determinants of delivery service use. *BMC Pregnancy Childbirth,* 9**,** 34.
GAGLIO, B., SHOUP, J. A. & GLASGOW, R. E. 2013. The RE-AIM Framework: A Systematic Review of Use Over Time. *American Journal of Public Health,* 103**,** e38-e46.
GAIESKI, D. F., MIKKELSEN, M. E., BAND, R. A., PINES, J. M., MASSONE, R., FURIA, F. F., SHOFER, F. S. & GOYAL, M. 2010. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med,* 38**,** 1045-53.
GALE, N. K., HEATH, G., CAMERON, E., RASHID, S. & REDWOOD, S. 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology,* 13**,** 117-117.
GALLOS, I. D., WILLIAMS, H. M., PRICE, M. J., MERRIEL, A., GEE, H., LISSAUER, D., MOORTHY, V., TOBIAS, A., DEEKS, J. J., WIDMER, M., TUNCALP, O., GULMEZOGLU, A. M., HOFMEYR, G. J. & COOMARASAMY, A. 2018. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. *Cochrane Database Syst Rev,* 4**,** Cd011689.
GANCHIMEG, T., OTA, E., MORISAKI, N., LAOPAIBOON, M., LUMBIGANON, P., ZHANG, J., YAMDAMSUREN, B., TEMMERMAN, M., SAY, L., TUNCALP, O., VOGEL, J. P., SOUZA, J. P. & MORI, R. 2014. Pregnancy and childbirth outcomes among adolescent mothers: a World Health Organization multicountry study. *British Journal of Obstetrics and Gynaecology,* 121 Suppl 1**,** 40-8.
GAO, H., MCDONNELL, A., HARRISON, D. A., MOORE, T., ADAM, S., DALY, K., ESMONDE, L., GOLDHILL, D. R., PARRY, G. J., RASHIDIAN, A., SUBBE, C. P. & HARVEY, S. 2007. Systematic review and evaluation of physiological track and trigger warning systems for identifying at-risk patients on the ward. *Intensive Care Med,* 33**,** 667-79.

GBANGBADE, S., HARVEY, SA, EDSON, W, BURKHALTER, B, AND ANTONAKOS, C. 2003. Safe motherhood studies: results from Benin. . Bethesda; USA.
GEREIN, N., GREEN, A. & PEARSON, S. 2006. The Implications of Shortages of Health Professionals for Maternal Health in Sub-Saharan Africa. *Reproductive Health Matters,* 14**,** 40-50.
GERRY, S., BIRKS, J., BONNICI, T., WATKINSON, P. J., KIRTLEY, S. & COLLINS, G. S. 2017. Early warning scores for detecting deterioration in adult hospital patients: a systematic review protocol. *BMJ Open,* 7**,** e019268.
GIMBEL, S., RUSTAGI, A. S., ROBINSON, J., KOUYATE, S., COUTINHO, J., NDUATI, R., PFEIFFER, J., GLOYD, S., SHERR, K., GRANATO, S. A., KONE, A., CRUZ, E., MANUEL, J. L., ZUCULE, J., NAPUA, M., MBATIA, G., WARIUA, G. & MAINA, M. 2016. Evaluation of a Systems Analysis and Improvement Approach to Optimize Prevention of Mother-To-Child Transmission of HIV Using the Consolidated Framework for Implementation Research. *J Acquir Immune Defic Syndr,* 72 Suppl 2**,** S108-16.
GIORDANO, J. C., PARPINELLI, M. A., CECATTI, J. G., HADDAD, S. M., COSTA, M. L., SURITA, F. G., PINTO E SILVA, J. L. & SOUSA, M. H. 2014. The Burden of Eclampsia: Results from a Multicenter Study on Surveillance of Severe Maternal Morbidity in Brazil. *PLoS ONE,* 9**,** e97401.
GLASGOW, R. E., LICHTENSTEIN, E. & MARCUS, A. C. 2003. Why don't we see more translation of health promotion research to practice? Rethinking the efficacy-to-effectiveness transition. *Am J Public Health,* 93**,** 1261-7.
GLASGOW, R. E., VOGT, T. M. & BOLES, S. M. 1999. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health,* 89.
GLOBAL HEALTH WORKFORCE ALLIANCE, W. H. O. 2010. Global Experience of Community Health Workers for Delivery of Health Related Millennium Development Goals: A Systematic Review, Country Case Studies, and Recommendations for Integration into National Health Systems. Geneva, Switzerland.
GRANT, A., TREWEEK, S., DREISCHULTE, T., FOY, R. & GUTHRIE, B. 2013. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. *Trials,* 14**,** 15.
GREENHALGH, T., ROBERT, G., MACFARLANE, F., BATE, P. & KYRIAKIDOU, O. 2004. Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Q,* 82.
GUINN, D. A., ABEL, D. E. & TOMLINSON, M. W. 2007. Early Goal Directed Therapy for Sepsis During Pregnancy. *Obstetrics and Gynecology Clinics of North America,* 34**,** 459-479.
GÜLMEZOGLU, A. M., SAY, L., BETRÁN, A. P., VILLAR, J. & PIAGGIO, G. 2004. WHO systematic review of maternal mortality and morbidity: methodological issues and challenges. *BMC Medical Research Methodology,* 4**,** 16.
HANCOCK, A., WEEKS, A. D. & LAVENDER, D. T. 2015. Is accurate and reliable blood loss estimation the 'crucial step' in early detection of postpartum haemorrhage: an integrative review of the literature. *BMC Pregnancy and Childbirth,* 15**,** 230.
HANNAH L NATHAN, H. B., KHATIA MUNGUAMBE, ESPERANÇA SEVENE, DAVID AKEJU, OLALEKAN O ADETORO, UMESH CHARANTHIMATH, MRUTYUNJAYA B BELLAD, ANNEMARIE DE GREEFF, JOHN ANTHONY, DAVID R HALL, WILHELM STEYN, MARIANNE VIDLER, PETER VON DADELSZEN, LUCY C CHAPPELL, JANE SANDALL, ANDREW H SHENNAN AND THE CLIP WORKING GROUP 2018. The CRADLE Vital Signs Alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings. *BMC Reproductive Health,* (In Press).
HARVEY, S. A., AYABACA, P., BUCAGU, M., DJIBRINA, S., EDSON, W. N., GBANGBADE, S., MCCAW-BINNS, A. & BURKHALTER, B. R. 2004. Skilled birth attendant competence: an initial assessment in four countries, and implications for the Safe Motherhood movement. *International Journal of Gynecology & Obstetrics,* 87**,** 203-210.
HAWE, P., SHIELL, A., RILEY, T. & GOLD, L. 2004. Methods for exploring implementation variation and local context within a cluster randomised community intervention trial. *Journal of Epidemiology and Community Health,* 58**,** 788.
HEDRIANA, H. L., WIESNER, S., DOWNS, B. G., PELLETREAU, B. & SHIELDS, L. E. 2016. Baseline assessment of a hospital-specific early warning trigger system for reducing maternal morbidity. *Int J Gynaecol Obstet,* 132**,** 337-41.
HEMMING K, G. A. 2014a. A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. . *Stata Journal.,* 14**,** 363-80.
HEMMING K, G. A., HAINES T, LILFORD R 2014b. Protocol: Consort extension to stepped wedge cluster randomised controlled trial. Equator Network.

HEMMING, K., HAINES, T. P., CHILTON, P. J., GIRLING, A. J. & LILFORD, R. J. 2015. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ : British Medical Journal,* 350.

HIRSCHHORN, L. R., SEMRAU, K., KODKANY, B., CHURCHILL, R., KAPOOR, A., SPECTOR, J., RINGER, S., FIRESTONE, R., KUMAR, V. & GAWANDE, A. 2015. Learning before leaping: integration of an adaptive study design process prior to initiation of BetterBirth, a large-scale randomized controlled trial in Uttar Pradesh, India. *Implementation Science,* 10**,** 117.

HODGKINSON, J. A., TUCKER, K. L., CRAWFORD, C., GREENFIELD, S. M., HENEGHAN, C., HINTON, L., KHAN, K., LOCOCK, L., MACKILLOP, L., MCCOURT, C., SELWOOD, M. & MCMANUS, R. J. 2014. Is self monitoring of blood pressure in pregnancy safe and effective? *BMJ : British Medical Journal,* 349.

HOFFMANN, T. C., ERUETI, C. & GLASZIOU, P. P. 2013. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *BMJ : British Medical Journal,* 347.

HOFFMANN, T. C., GLASZIOU, P. P., BOUTRON, I., MILNE, R., PERERA, R., MOHER, D., ALTMAN, D. G., BARBOUR, V., MACDONALD, H., JOHNSTON, M., LAMB, S. E., DIXON-WOODS, M., MCCULLOCH, P., WYATT, J. C., CHAN, A.-W. & MICHIE, S. 2014. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ : British Medical Journal,* 348.

HOUNTON, S., CHAPMAN, G., MENTEN, J., DE BROUWERE, V., ENSOR, T., SOMBIE, I., MEDA, N. & RONSMANS, C. 2008. Accessibility and utilisation of delivery care within a Skilled Care Initiative in rural Burkina Faso. *Trop Med Int Health,* 13 Suppl 1**,** 44-52.

HUSSEIN, J., KANGURU, L., ASTIN, M. & MUNJANJA, S. 2012. The effectiveness of emergency obstetric referral interventions in developing country settings: a systematic review. *PLoS Med,* 9**,** e1001264.

HUSSEY, M. A. H., J. P. 2007. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials.* United States.

ISAACS, R. A., WEE, M. Y., BICK, D. E., BEAKE, S., SHEPPARD, Z. A., THOMAS, S., HUNDLEY, V., SMITH, G. B., VAN TEIJLINGEN, E. & THOMAS, P. W. 2014. A national survey of obstetric early warning systems in the United Kingdom: five years on. *Anaesthesia,* 69**,** 687-92.

JACOBS, C., MICHELO, C., CHOLA, M., OLIPHANT, N., HALWIINDI, H., MASWENYEHO, S., BABOO, K. S. & MOSHABELA, M. 2018. Evaluation of a community-based intervention to improve maternal and neonatal health service coverage in the most rural and remote districts of Zambia. *PLOS ONE,* 13**,** e0190145.

JENNINGS, L., YEBADOKPO, A. S., AFFO, J., AGBOGBE, M. & TANKOANO, A. 2011. Task shifting in maternal and newborn care: a non-inferiority study examining delegation of antenatal counseling to lay nurse aides supported by job aids in Benin. *Implementation Science : IS,* 6**,** 2-2.

KARIM, A. M., ADMASSU, K., SCHELLENBERG, J., ALEMU, H., GETACHEW, N., AMEHA, A., TADESSE, L. & BETEMARIAM, W. 2013. Effect of ethiopia's health extension program on maternal and newborn health care practices in 101 rural districts: a dose-response study. *PLoS One,* 8**,** e65160.

KASSEBAUM, N. J., BERTOZZI-VILLA, A., COGGESHALL, M. S., SHACKELFORD, K. A., STEINER, C., HEUTON, K. R., GONZALEZ-MEDINA, D., BARBER, R., HUYNH, C., DICKER, D., TEMPLIN, T., WOLOCK, T. M., OZGOREN, A. A., ABD-ALLAH, F., ABERA, S. F., ABUBAKAR, I., ACHOKI, T., ADELEKAN, A., ADEMI, Z., ADOU, A. K., ADSUAR, J. C., AGARDH, E. E., AKENA, D., ALASFOOR, D., ALEMU, Z. A., ALFONSO-CRISTANCHO, R., ALHABIB, S., ALI, R., AL KAHBOURI, M. J., ALLA, F., ALLEN, P. J., ALMAZROA, M. A., ALSHARIF, U., ALVAREZ, E., ALVIS-GUZMÁN, N., AMANKWAA, A. A., AMARE, A. T., AMINI, H., AMMAR, W., ANTONIO, C. A. T., ANWARI, P., ÄRNLÖV, J., ARSENIJEVIC, V. S. A., ARTAMAN, A., ASAD, M. M., ASGHAR, R. J., ASSADI, R., ATKINS, L. S., BADAWI, A., BALAKRISHNAN, K., BASU, A., BASU, S., BEARDSLEY, J., BEDI, N., BEKELE, T., BELL, M. L., BERNABE, E., BEYENE, T. J., BHUTTA, Z., ABDULHAK, A. B., BLORE, J. D., BASARA, B. B., BOSE, D., BREITBORDE, N., CÁRDENAS, R., CASTAÑEDA-ORJUELA, C. A., CASTRO, R. E., CATALÁ-LÓPEZ, F., CAVLIN, A., CHANG, J.-C., CHE, X., CHRISTOPHI, C. A., CHUGH, S. S., CIRILLO, M., COLQUHOUN, S. M., COOPER, L. T., COOPER, C., DA COSTA LEITE, I., DANDONA, L., DANDONA, R., DAVIS, A., DAYAMA, A., DEGENHARDT, L., DE LEO, D., DEL POZO-CRUZ, B., DERIBE, K., DESSALEGN, M., DEVEBER, G. A., DHARMARATNE, S. D., DILMEN, U., DING, E. L., DORRINGTON, R. E., DRISCOLL, T. R., ERMAKOV, S. P., ESTEGHAMATI, A., FARAON, E. J. A., FARZADFAR, F., FELICIO, M. M.,

FERESHTEHNEJAD, S.-M., DE LIMA, G. M. F., et al. 2013. Global, Regional, and National Levels and Causes of Maternal Mortality during 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 384.9947 (2014): 980–1004. *PMC* . Web. 11 Nov. 2016. *Lancet,* 384**,** 980-1004.

KENNY, L. C., BLACK, M. A., POSTON, L., TAYLOR, R., MYERS, J. E., BAKER, P. N., MCCOWAN, L. M., SIMPSON, N. A., DEKKER, G. A., ROBERTS, C. T., RODEMS, K., NOLAND, B., RAYMUNDO, M., WALKER, J. J. & NORTH, R. A. 2014. Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: the Screening for Pregnancy Endpoints (SCOPE) international cohort study. *Hypertension,* 64**,** 644-52.

KENZAKA, T., OKAYAMA, M., KUROKI, S., FUKUI, M., YAHATA, S., HAYASHI, H., KITAO, A., SUGIYAMA, D., KAJII, E. & HASHIMOTO, M. 2012. Importance of vital signs to the early diagnosis and severity of sepsis: association between vital signs and sequential organ failure assessment score in patients with sepsis. *Intern Med,* 51**,** 871-6.

KHAN, K. S., WOJDYLA, D., SAY, L., GULMEZOGLU, A. M. & VAN LOOK, P. F. 2006. WHO analysis of causes of maternal death: a systematic review. *Lancet.* England.

KHOWAJA, A. R., QURESHI, R. N., SAWCHUCK, D., OLADAPO, O. T., ADETORO, O. O., ORENUGA, E. A., BELLAD, M., MALLAPUR, A., CHARANTIMATH, U., SEVENE, E., MUNGUAMBE, K., BOENE, H. E., VIDLER, M., BHUTTA, Z. A., VON DADELSZEN, P. & GROUP, C. W. 2016. The feasibility of community level interventions for pre-eclampsia in South Asia and Sub-Saharan Africa: a mixed-methods design. *Reproductive Health,* 13**,** 56.

KIKUCHI, K., ANSAH, E., OKAWA, S., SHIBANUMA, A., GYAPONG, M., OWUSU-AGYEI, S., ODURO, A., QUANSAH-ASARE, G., HODGSON, A. & JIMBA, M. 2015. Ghana's Ensure Mothers and Babies Regular Access to Care (EMBRACE) program: study protocol for a cluster randomized controlled trial. *Trials,* 16**,** 22.

KILBOURNE, A. M., NEUMANN, M. S., PINCUS, H. A., BAUER, M. S. & STALL, R. 2007. Implementing evidence-based interventions in health care: application of the replicating effective programs framework. *Implement Sci,* 2.

KIRBY, D. 2004. *BDI Logic models: A useful tool for designing, strengthening and evaluating programs to reduce adolescent sexual risk taking, pregnancy, HIV and other STDs* [Online]. Available: http://recapp.etr.org/recapp/documents/BDILOGICMODEL20030924.pdf [Accessed 14th June 2017].

KNAPP, G. & HARTUNG, J. 2003. Improved tests for a random effects meta-regression with a single covariate. *Stat Med,* 22**,** 2693-710.

KNIGHT M, K. S., BROCKLEHURST P, NEILSON J, SHAKESPEARE J, KURINCZUK J: ON BEHALF OF MBRRACE-UK. 2014. Saving Lives, Improving Mothers' Care: lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and Morbidity 2009–2012. Oxford: National Perinatal Epidemiology Unit, .

KNIGHT M, N. M., TUFFNELL D, KENYON S, SHAKESPEARE J, BROCKLEHURST P, KURINCZUK JJ (EDS.) ON BEHALF OF MBRRACE-UK. 2016. Saving Lives, Improving Mothers' Care - Surveillance of maternal deaths in the UK 2012-14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-14.

KNIGHT M, N. M., TUFFNELL D, SHAKESPEARE J, KENYON S, KURINCZUK JJ (EDS.) ON BEHALF OF MBRRACE-UK. 2017. Saving Lives, Improving Mother's Care- Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013-15.

KOHN, J. R., DILDY, G. A. & EPPES, C. S. 2018. Shock index and delta-shock index are superior to existing maternal early warning criteria to identify postpartum hemorrhage and need for intervention. *J Matern Fetal Neonatal Med***,** 1-7.

KOOPMANS, C. M., BIJLENGA, D., GROEN, H., VIJGEN, S. M., AARNOUDSE, J. G., BEKEDAM, D. J., VAN DEN BERG, P. P., DE BOER, K., BURGGRAAFF, J. M., BLOEMENKAMP, K. W., DROGTROP, A. P., FRANX, A., DE GROOT, C. J., HUISJES, A. J., KWEE, A., VAN LOON, A. J., LUB, A., PAPATSONIS, D. N., VAN DER POST, J. A., ROUMEN, F. J., SCHEEPERS, H. C., WILLEKES, C., MOL, B. W. & VAN PAMPUS, M. G. 2009. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet,* 374**,** 979-88.

KOOPMANS, C. M., VAN DER TUUK, K., GROEN, H., DOORNBOS, J. P., DE GRAAF, I. M., VAN DER SALM, P. C., PORATH, M. M., KUPPENS, S. M., WIJNEN, E. J.,

AARDENBURG, R., VAN LOON, A. J., AKERBOOM, B. M., VAN DER LANS, P. J., MOL, B. W. & VAN PAMPUS, M. G. 2014. Prediction of postpartum hemorrhage in women with gestational hypertension or mild preeclampsia at term. *Acta Obstet Gynecol Scand,* 93**,** 399-407.

KOURTIS, A. P., READ, J. S. & JAMIESON, D. J. 2014. Pregnancy and infection. *N Engl J Med,* 370**,** 2211-8.

KRAMER, H. M., SCHUTTE, J. M., ZWART, J. J., SCHUITEMAKER, N. W., STEEGERS, E. A. & VAN ROOSMALEN, J. 2009. Maternal mortality and severe morbidity from sepsis in the Netherlands. *Acta Obstet Gynecol Scand,* 88**,** 647-53.

KRISTUNAS, C., MORRIS, T. & GRAY, L. 2017. Unequal cluster sizes in stepped-wedge cluster randomised trials: a systematic review. *BMJ Open,* 7**,** e017151.

KUMAR, F., KEMP, J., EDWARDS, C., PULLON, R. M., LOERUP, L., TRIANTAFYLLIDIS, A., SALVI, D., GIBSON, O., GERRY, S., MACKILLOP, L. H., TARASSENKO, L. & WATKINSON, P. J. 2017. Pregnancy physiology pattern prediction study (4P study): protocol of an observational cohort study collecting vital sign information to inform the development of an accurate centile-based obstetric early warning score. *BMJ Open,* 7**,** e016034.

KUNG'U, J., NDIAYE, B., NDEDDA, C., MAMO, G., NDIAYE, M., PENDAME, R., NEUFELD, L., MWITARI, J., DESTA, H., DIOP, M., DOUDOU, M. & DE-REGIL, L. 2018. Design and implementation of a health systems strengthening approach to improve health and nutrition of pregnant women and newborns in Ethiopia, Kenya, Niger, and Senegal. *Maternal & Child Nutrition,* 14**,** e12533.

LAPPEN, J. R., KEENE, M., LORE, M., GROBMAN, W. A. & GOSSETT, D. R. 2010. Existing models fail to predict sepsis in an obstetric population with intrauterine infection. *American Journal of Obstetrics & Gynecology,* 203**,** 573.e1-573.e5.

LASSI, Z. S. & BHUTTA, Z. A. 2015. Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes. *Cochrane Database of Systematic Reviews*.

LAURANT, M., REEVES, D., HERMENS, R., BRASPENNING, J., GROL, R. & SIBBALD, B. 2005. Substitution of doctors by nurses in primary care. *Cochrane Database of Systematic Reviews*.

LE BAS, A., CHANDRAHARAN, E., ADDEI, A. & ARULKUMARAN, S. 2014. Use of the "obstetric shock index" as an adjunct in identifying significant blood loss in patients with massive postpartum hemorrhage. *International Journal of Gynecology & Obstetrics,* 124**,** 253-255.

LEFFERT, L. R., CLANCY, C. R., BATEMAN, B. T., BRYANT, A. S. & KUKLINA, E. V. 2015. Hypertensive Disorders and Pregnancy-Related Stroke: Frequency, Trends, Risk Factors, and Outcomes. *Obstetrics and gynecology,* 125**,** 124-131.

LEHMAN, W. E., SIMPSON, D. D., KNIGHT, D. K. & FLYNN, P. M. 2011. Integration of treatment innovation planning and implementation: strategic process models and organizational challenges. *Psychol Addict Behav,* 25.

LESLIE, H. H., SUN, Z. & KRUK, M. E. 2017. Association between infrastructure and observed quality of care in 4 healthcare services: A cross-sectional study of 4,300 facilities in 8 countries. *PLOS Medicine,* 14**,** e1002464.

LEWIN, S., MUNABI-BABIGUMIRA, S., GLENTON, C., DANIELS, K., BOSCH-CAPBLANCH, X., VAN WYK, B. E., ODGAARD-JENSEN, J., JOHANSEN, M., AJA, G. N., ZWARENSTEIN, M. & SCHEEL, I. B. 2010. Lay health workers in primary and community health care for maternal and child health and the management of infectious diseases. *Cochrane Database of Systematic Reviews*.

LEWIS, G. 2007. The Confidential Enquiry into Materna and Child Health (CEMACH). Saving Mothers Live's: reviewing maternal deaths to make motherhood safer - 2003-2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *In:* CEMACH (ed.). London.

LIN, V. 2016. Pulse Signal Plot for the CRADLE Vital Sign Alert. *In:* MICROLIFE (ed.).

LINNAN L, S. A. 2002. Process evaluation for public health interventions and research. . California: Jossey-Bass San Francisco; .

LOERUP, L., PULLON, R. M., BIRKS, J., FLEMING, S., MACKILLOP, L. H. & WATKINSON, P. J. 2016. Trends of vital signs with gestational age in normal pregnancies: a systematic review protocol. *BMJ Open,* 6**,** e008769.

LOUDON, K., TREWEEK, S., SULLIVAN, F., DONNAN, P., THORPE, K. E. & ZWARENSTEIN, M. 2015. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ : British Medical Journal,* 350.

MABIE, W. C., BARTON, J. R. & SIBAI, B. 1997. Septic shock in pregnancy. *Obstet Gynecol,* 90**,** 553-61.

MACKINTOSH, N., WATSON, K., RANCE, S. & SANDALL, J. 2014. Value of a modified early obstetric warning system (MEOWS) in managing maternal complications in the peripartum period: an ethnographic study. *BMJ Qual Saf,* 23**,** 26-34.
MAGEE, L. A., HELEWA, M. & REY, E. 2008. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can,* 30**,** S1-s2.
MAGUIRE, P. J., O'HIGGINS, A. C., POWER, K. A., DALY, N., MCKEATING, A. & TURNER, M. J. 2015. Maternal bacteremia and the Irish maternity early warning system. *Int J Gynaecol Obstet,* 129**,** 142-5.
MAJOKO, F., NYSTROM, L., MUNJANJA, S. P. & LINDMARK, G. 2005. Effectiveness of referral system for antenatal and intra-partum problems in Gutu district, Zimbabwe. *J Obstet Gynaecol,* 25**,** 656-61.
MARTIN, J., TALJAARD, M., GIRLING, A. & HEMMING, K. 2016. Systematic review finds major deficiencies in sample size methodology and reporting for stepped-wedge cluster randomised trials. *BMJ Open,* 6**,** e010166.
MARTIN, J. N., JR., THIGPEN, B. D., MOORE, R. C., ROSE, C. H., CUSHMAN, J. & MAY, W. 2005. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol,* 105**,** 246-54.
MARU, S., NIROLA, I., THAPA, A., THAPA, P., KUNWAR, L., WU, W.-J., HALLIDAY, S., CITRIN, D., SCHWARZ, R., BASNETT, I., KC, N., KARKI, K., CHAUDHARI, P. & MARU, D. 2018. An integrated community health worker intervention in rural Nepal: a type 2 hybrid effectiveness-implementation study protocol. *Implementation Science : IS,* 13**,** 53.
MAY, C. & FINCH, T. 2009. Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory. *Sociology,* 43**,** 535-554.
MAYHEW, M., HANSEN, P. M., PETERS, D. H., EDWARD, A., SINGH, L. P., DWIVEDI, V., MASHKOOR, A. & BURNHAM, G. 2008. Determinants of Skilled Birth Attendant Utilization in Afghanistan: A Cross-Sectional Study. *American Journal of Public Health,* 98**,** 1849-1856.
MAZUMDER, S., UPADHYAY, R. P., HILL, Z., TANEJA, S., DUBE, B., KAUR, J., SHEKHAR, M., GHOSH, R., BISHT, S., MARTINES, J. C., BAHL, R., SOMMERFELT, H. & BHANDARI, N. 2018. Kangaroo mother care: using formative research to design an acceptable community intervention. *BMC Public Health,* 18**,** 307.
MBIZVO, M. T., FAWCUS, S., LINDMARK, G. & NYSTROM, L. 1993. Maternal mortality in rural and urban Zimbabwe: social and reproductive factors in an incident case-referent study. *Soc Sci Med,* 36**,** 1197-205.
MCCARNEY, R., WARNER, J., ILIFFE, S., VAN HASELEN, R., GRIFFIN, M. & FISHER, P. 2007. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol,* 7**,** 30.
MCCARTHY, J. & MAINE, D. 1992. A framework for analyzing the determinants of maternal mortality. *Stud Fam Plann,* 23**,** 23-33.
MCCAW-BINNS, A., BURKHALTER, B, EDSON, W, HARVEY, SA, AND ANTONAKOS, C. 2004. Safe motherhood studies: results from Jamaica. *Quality Assurance Project.* Bethesda; USA.
MCCAW-BINNS, A. M., ASHLEY, D. E., KNIGHT, L. P., MACGILLIVRAY, I. & GOLDING, J. 2004. Strategies to prevent eclampsia in a developing country: I. Reorganization of maternity services. *Int J Gynaecol Obstet,* 87**,** 286-94.
MCKIBBON, K. A., LOKKER, C., WILCZYNSKI, N. L., CILISKA, D., DOBBINS, M., DAVIS, D. A., HAYNES, R. B. & STRAUS, S. E. 2010. A cross-sectional study of the number and frequency of terms used to refer to knowledge translation in a body of health literature in 2006: a Tower of Babel? *Implement Sci,* 5**,** 16.
MDEGE, N. D., MAN, M. S., TAYLOR NEE BROWN, C. A. & TORGERSON, D. J. 2011. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. *J Clin Epidemiol,* 64**,** 936-48.
MERDAD, L. & ALI, M. M. 2018. Timing of maternal death: Levels, trends, and ecological correlates using sibling data from 34 sub-Saharan African countries. *PLoS ONE,* 13**,** e0189416.
MERRIEL, A., MUROVE BOBB, T., MERRIEL SAMUEL, W. D., SIBANDA, T., MOYO, S. & CROFTS, J. 2016. Implementation of a modified obstetric early warning system to improve the quality of obstetric care in Zimbabwe. *International Journal of Gynecology & Obstetrics,* 136**,** 175-179.
MGAWADERE, F., UNKELS, R. & VAN DEN BROEK, N. 2016. Assigning cause of maternal death: a comparison of findings by a facility-based review team, an expert panel using the new ICD-MM cause classification and a computer-based program (InterVA-4). *BJOG: An International Journal of Obstetrics & Gynaecology,* 123**,** 1647-1653.

MICHIE, S., FIXSEN, D., GRIMSHAW, J. M. & ECCLES, M. P. 2009. Specifying and reporting complex behaviour change interventions: the need for a scientific method. *Implementation Science : IS,* 4**,** 40-40.

MIDHET, F. & BECKER, S. 2010. Impact of community-based interventions on maternal and neonatal health indicators: Results from a community randomized trial in rural Balochistan, Pakistan. *Reprod Health,* 7**,** 30.

MINISTRY OF HEALTH AND SOCIAL WELFARE TANZANIA, M. O. H. Z., NATIONAL BUREAU OF STATISTIC, OFFICE OF THE CHIEF GOVERNMENT STATITICIAN AND ICF INTERNATIONAL 2014-2015. Tanzania Service Provision Assessment Survey. Dar ed Salaam, Tanzania and Rockville, Maryland USA.

MITCHELL, C., MEREDITH, P., RICHARDSON, M., GREENGROSS, P. & SMITH, G. B. 2016. Reducing the number and impact of outbreaks of nosocomial viral gastroenteritis: time-series analysis of a multidimensional quality improvement initiative. *BMJ Quality & Safety,* 25**,** 466-474.

MODI, D., GOPALAN, R., SHAH, S., VENKATRAMAN, S., DESAI, G., DESAI, S. & SHAH, P. 2015. Development and formative evaluation of an innovative mHealth intervention for improving coverage of community-based maternal, newborn and child health services in rural areas of India. *Glob Health Action,* 8**,** 26769.

MOHAMMED, M., HAYTON, R., CLEMENTS, G., SMITH, G. & PRYTHERCH, D. 2009. Improving accuracy and efficiency of early warning scores in acute care. *Br J Nurs,* 18**,** 18-24.

MOL, B. W. J., ROBERTS, C. T., THANGARATINAM, S., MAGEE, L. A., DE GROOT, C. J. M. & HOFMEYR, G. J. 2016. Pre-eclampsia. *The Lancet,* 387**,** 999-1011.

MOORE, G. F., AUDREY, S., BARKER, M., BOND, L., BONELL, C., HARDEMAN, W., MOORE, L., O'CATHAIN, A., TINATI, T., WIGHT, D. & BAIRD, J. 2015. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ,* 350.

MOORE, S. C., MURPHY, S., MOORE, S. N., BRENNAN, I., BYRNE, E., SHEPHERD, J. & MOORE, L. 2012. An exploratory randomised controlled trial of a premises-level intervention to reduce alcohol-related harm including violence in the United Kingdom. *BMC Public Health,* 12**,** 412-412.

MORRISON, J., OSRIN, D., SHRESTHA, B., TUMBAHANGPHE, K. M., TAMANG, S., SHRESTHA, D., THAPA, S., MESKO, N., MANANDHAR, D. S. & COSTELLO, A. 2008. How did formative research inform the development of a women's group intervention in rural Nepal? *Journal of perinatology : official journal of the California Perinatal Association,* 28**,** S14-S22.

MOULLIN, J. C., SABATER-HERNANDEZ, D., FERNANDEZ-LLIMOS, F. & BENRIMOJ, S. I. 2015. A systematic review of implementation frameworks of innovations in healthcare and resulting generic implementation framework. *Health Res Policy Syst,* 13**,** 16.

MUNRO, A. & BLOOR, M. 2010. Process evaluation: the new miracle ingredient in public health research? *Qualitative Research,* 10**,** 699-713.

MURRAY, S. F., DAVIES, S., PHIRI, R. K. & AHMED, Y. 2001. Tools for monitoring the effectiveness of district maternity referral systems. *Health Policy Plan,* 16**,** 353-61.

MYATT, L., CLIFTON, R. G., ROBERTS, J. M., SPONG, C. Y., WAPNER, R. J., THORP, J. M., MERCER, B. M., PEACEMAN, A. M., RAMIN, S. M., CARPENTER, M. W., SCISCIONE, A., TOLOSA, J. E., SAADE, G., SOROKIN, Y. & ANDERSON, G. D. 2013. Can changes in angiogenic biomarkers between the first and second trimesters of pregnancy predict development of pre-eclampsia in a low-risk nulliparous patient population? *BJOG: An International Journal of Obstetrics & Gynaecology,* 120**,** 1183-1191.

NAIR, M., CHOUDHURY, M. K., CHOUDHURY, S. S., KAKOTY, S. D., SARMA, U. C., WEBSTER, P. & KNIGHT, M. 2016. Association between maternal anaemia and pregnancy outcomes: a cohort study in Assam, India. *BMJ global health,* 1**,** e000026-e000026.

NATHAN, H. L., BOENE, H., MUNGUAMBE, K., SEVENE, E., AKEJU, D., ADETORO, O. O., CHARANTHIMATH, U., BELLAD, M. B., DE GREEFF, A., ANTHONY, J., HALL, D. R., STEYN, W., VIDLER, M., VON DADELSZEN, P., CHAPPELL, L. C., SANDALL, J. & SHENNAN, A. H. 2018a. The CRADLE vital signs alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings. *Reprod Health,* 15**,** 5.

NATHAN, H. L., DE GREEFF, A., HEZELGRAVE, N. L., CHAPPELL, L. C. & SHENNAN, A. H. 2015a. Accuracy validation of the Microlife 3AS1-2 blood pressure device in a pregnant population with low blood pressure. *Blood Press Monit,* 20**,** 299-302.

NATHAN, H. L., DE GREEFF, A., HEZELGRAVE, N. L., CHAPPELL, L. C. & SHENNAN, A. H. 2015b. An accurate semiautomated oscillometric blood pressure device for use in

pregnancy (including pre-eclampsia) in a low-income and middle-income country population: the Microlife 3AS1-2. *Blood Press Monit,* 20**,** 52-5.
NATHAN, H. L., DUHIG, K., VOUSDEN, N., LAWLEY, E., SEED, P. T., SANDALL, J., BELLAD, M. B., BROWN, A. C., CHAPPELL, L. C., GOUDAR, S. S., GIDIRI, M. F. & SHENNAN, A. H. 2018b. Evaluation of a novel device for the management of high blood pressure and shock in pregnancy in low-resource settings: study protocol for a stepped-wedge cluster-randomised controlled trial (CRADLE-3 trial). *Trials,* 19**,** 206.
NATHAN, H. L., EL AYADI, A., HEZELGRAVE, N. L., SEED, P., BUTRICK, E., MILLER, S., BRILEY, A., BEWLEY, S. & SHENNAN, A. H. 2015c. Shock index: an effective predictor of outcome in postpartum haemorrhage? *BJOG,* 122**,** 268-75.
NATHAN, H. L., SEED, P. T., HEZELGRAVE, N. L., DE GREEFF, A., LAWLEY, E., ANTHONY, J., HALL, D. R., STEYN, W., CHAPPELL, L. C. & SHENNAN, A. H. 2017. Early warning system hypertension thresholds to predict adverse outcomes in pre-eclampsia: A prospective cohort study. *Pregnancy Hypertens*.
NATHAN, H. V., N; LAWLEY, E; DE GREEFF ANNEMARIE, HEZELGRAVE, NL; SLOAN, N; TANNA, N; GOUDAR, SS; GIDIRI, MF; SANDALL, J; CHAPPELL, LC & SHENNAN, A 2018. Development and evaluation of a novel Vital Signs Alert device for use in pregnancy in low-resource settings. *BMJ Innovations,* 0.
NATIONAL CONFIDENTIAL ENQUIRY INTO PATIENT OUTCOME AND DEATH 2005. National confidential enquiry into patient outcomes and death. An acute problem? London.
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2010. *Hypertension in pregnancy: diagnosis and management* [Online]. NICE. Available: https://www.nice.org.uk/guidance/cg107/resources/hypertension-in-pregnancy-diagnosis-and-management-pdf-35109334011877 [Accessed 26th June 2018].
NATIONAL STATISTICAL OFFICE [MALAWI] AND ICF. 2017. *Malawi Demographic and Helath Survey 2015-16* [Online]. Zomba, Malawi and Rockville, Maryland, USA: National Statistical Office and ICF. Available: https://dhsprogram.com/pubs/pdf/FR319/FR319.pdf [Accessed 24th January 2019].
NG, M., GAKIDOU, E., LEVIN-RECTOR, A., KHERA, A., MURRAY, C. J. & DANDONA, L. 2011. Assessment of population-level effect of Avahan, an HIV-prevention initiative in India. *Lancet,* 378**,** 1643-52.
NG'ANJO PHIRI, S., FYLKESNES, K., MOLAND, K. M., BYSKOV, J. & KISERUD, T. 2016. Rural-Urban Inequity in Unmet Obstetric Needs and Functionality of Emergency Obstetric Care Services in a Zambian District. *PLOS ONE,* 11**,** e0145196.
NICE. 2016. *NICE Clinical Guideline 51 Sepsis: recognition, diagnosis and early management: 1-50.* [Online]. [Accessed 30th January 2018].
NIEGSCH, M., FABRITIUS, M. L. & ANHOJ, J. 2013. Imperfect implementation of an early warning scoring system in a Danish teaching hospital: a cross-sectional study. *PLoS One,* 8**,** e70068.
NIETERT, P. J., WESSELL, A. M., FEIFER, C. & ORNSTEIN, S. M. 2006. Effect of terminal digit preference on blood pressure measurement and treatment in primary care. *Am J Hypertens,* 19**,** 147-52.
NORRIS, S. A., HO, J. C., RASHED, A. A., VINDING, V., SKAU, J. K., BIESMA, R., AAGAARD-HANSEN, J., HANSON, M. & MATZEN, P. 2016. Pre-pregnancy community-based intervention for couples in Malaysia: application of intervention mapping. *BMC Public Health,* 16**,** 1167.
NYAMTEMA, A. S., URASSA, D. P. & VAN ROOSMALEN, J. 2011. Maternal health interventions in resource limited countries: a systematic review of packages, impacts and factors for change. *BMC Pregnancy and Childbirth,* 11**,** 30.
O'BRIEN, E., ATKINS, N., STERGIOU, G., KARPETTAS, N., PARATI, G., ASMAR, R., IMAI, Y., WANG, J., MENGDEN, T. & SHENNAN, A. 2010. European Society of Hypertension International Protocol revision 2010 for the validation of blood pressure measuring devices in adults. *Blood Press Monit,* 15**,** 23-38.
O'BRIEN, E., PETRIE, J., LITTLER, W., DE SWIET, M., PADFIELD, P. L., ALTMAN, D. G., BLAND, M., COATS, A. & ATKINS, N. 1993. An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens,* 11**,** 677-9.
OUD, L. 2014. Pregnancy-Associated Severe Sepsis: Contemporary State and Future Challenges. *Infectious Diseases and Therapy,* 3**,** 175-189.
PATEL, A., GOUDAR, S. S., GELLER, S. E., KODKANY, B. S., EDLAVITCH, S. A., WAGH, K., PATTED, S. S., NAIK, V. A., MOSS, N. & DERMAN, R. J. 2006. Drape estimation vs. visual assessment for estimating postpartum hemorrhage. *Int J Gynaecol Obstet,* 93**,** 220-4.

PATERNINA-CAICEDO, A., MIRANDA, J., BOURJEILY, G., LEVINSON, A., DUENAS, C., BELLO-MUNOZ, C. & ROJAS-SUAREZ, J. A. 2017. Performance of the Obstetric Early Warning Score in critically ill patients for the prediction of maternal death. *Am J Obstet Gynecol,* 216**,** 58.e1-58.e8.

PAUL, B. K. & RUMSEY, D. J. 2002. Utilization of health facilities and trained birth attendants for childbirth in rural Bangladesh: an empirical study. *Soc Sci Med,* 54**,** 1755-65.

PAWSON R, T. N. 1997. *Realistic evaluation.,* London, Sage Publications.

PAYNE, B. A., HUTCHEON, J. A., ANSERMINO, J. M., HALL, D. R., BHUTTA, Z. A., BHUTTA, S. Z., BIRYABAREMA, C., GROBMAN, W. A., GROEN, H., HANIFF, F., LI, J., MAGEE, L. A., MERIALDI, M., NAKIMULI, A., QU, Z., SIKANDAR, R., SASS, N., SAWCHUCK, D., STEYN, D. W., WIDMER, M., ZHOU, J. & VON DADELSZEN, P. 2014. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. *PLoS Med,* 11**,** e1001589.

PEMBE, A. B., CARLSTEDT, A., URASSA, D. P., LINDMARK, G., NYSTRÖM, L. & DARJ, E. 2010. Effectiveness of maternal referral system in a rural setting: a case study from Rufiji district, Tanzania. *BMC Health Services Research,* 10**,** 326-326.

PENFOLD, S., SHAMBA, D., HANSON, C., JARIBU, J., MANZI, F., MARCHANT, T., TANNER, M., RAMSEY, K., SCHELLENBERG, D. & SCHELLENBERG, J. A. 2013. Staff experiences of providing maternity services in rural southern Tanzania – a focus on equipment, drug and supply issues. *BMC Health Services Research,* 13**,** 61-61.

PETERS, D. H., ADAM, T., ALONGE, O., AGYEPONG, I. A. & TRAN, N. 2013a. Implementation research: what it is and how to do it. *BMJ : British Medical Journal,* 347.

PETERS, D. H., TRAN, N. E. & ADAM, T. 2013b. Implementation Research in Health: A Practical Guide. Alliance for Health Policy and Systems Research, World Health Organization, .

PETERS, D. H. E.-S., SAMEH; SIADAT, BANAFSHEH; JANOVSKY, KATJA; VUJICIC, MARKO. 2009. Improving Health Service Delivery in Developing Countries : From Evidence to Action. . *Directions in Development; Human Development;.* Washington, DC: World Bank.: © World Bank.

PIRKLE, C. M., DUMONT, A. & ZUNZUNEGUI, M. V. 2011. Criterion-based clinical audit to assess quality of obstetrical care in low- and middle-income countries: a systematic review. *Int J Qual Health Care,* 23**,** 456-63.

POWELL, B. J., WALTZ, T. J., CHINMAN, M. J., DAMSCHRODER, L. J., SMITH, J. L., MATTHIEU, M. M., PROCTOR, E. K. & KIRCHNER, J. E. 2015. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implementation Science,* 10**,** 21.

PRASERTCHAROENSUK, W., SWADPANICH, U. & LUMBIGANON, P. 2000. Accuracy of the blood loss estimation in the third stage of labor. *International Journal of Gynecology & Obstetrics,* 71**,** 69-70.

PROCTOR, E., LUKE, D., CALHOUN, A., MCMILLEN, C., BROWNSON, R., MCCRARY, S. & PADEK, M. 2015. Sustainability of evidence-based healthcare: research agenda, methodological advances, and infrastructure support. *Implement Sci,* 10**,** 88.

PROCTOR, E., SILMERE, H., RAGHAVAN, R., HOVMAND, P., AARONS, G., BUNGER, A., GRIFFEY, R. & HENSLEY, M. 2011. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health,* 38**,** 65-76.

PRONYK, P. M., NEMSER, B., MALIQI, B., SPRINGSTUBB, N., SERA, D., KARIMOV, R., KATWAN, E., WALTER, B. & BIJLEVELD, P. 2016. The UN Commission on Life Saving Commodities 3 years on: global progress update and results of a multicountry assessment. *Lancet Glob Health,* 4**,** e276-86.

PULLINGER, R., WILSON, S., WAY, R., SANTOS, M., WONG, D., CLIFTON, D., BIRKS, J. & TARASSENKO, L. 2017. Implementing an electronic observation and early warning score chart in the emergency department: a feasibility study. *Eur J Emerg Med,* 24**,** e11-e16.

RABIN, B. A., BROWNSON, R. C., HAIRE-JOSHU, D., KREUTER, M. W. & WEAVER, N. L. 2008. A glossary for dissemination and implementation research in health. *J Public Health Manag Pract,* 14.

RADY, M. Y., RIVERS, E. P., MARTIN, G. B., SMITHLINE, H., APPELTON, T. & NOWAK, R. M. 1992. Continuous central venous oximetry and shock index in the emergency department: use in the evaluation of clinical shock. *Am J Emerg Med,* 10**,** 538-41.

RIDGEWAY, J. L., LEBLANC, A., BRANDA, M., HARMS, R. W., MORRIS, M. A., NESBITT, K., GOSTOUT, B. S., BARKEY, L. M., SOBOLEWSKI, S. M., BRODRICK, E., INSELMAN, J., BARON, A., SIVLY, A., BAKER, M., FINNIE, D., CHAUDHRY, R. & FAMUYIDE, A. O. 2015. Implementation of a new prenatal care model to reduce office visits and increase

connectivity and continuity of care: protocol for a mixed-methods study. *BMC Pregnancy and Childbirth,* 15**,** 323.
RITCHIE J, L. J. 2003. *Qualitative research practice: a guide for social science students and researchers.,* London, Sage.
RIVERS, E., NGUYEN, B., HAVSTAD, S., RESSLER, J., MUZZIN, A., KNOBLICH, B., PETERSON, E. & TOMLANOVICH, M. 2001. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *New England Journal of Medicine,* 345**,** 1368-1377.
RONSMANS, C. & CAMPBELL, O. 2011. Quantifying the fall in mortality associated with interventions related to hypertensive diseases of pregnancy. *BMC Public Health,* 11**,** S8-S8.
RONSMANS, C. & GRAHAM, W. J. 2006. Maternal mortality: who, when, where, and why. *Lancet,* 368**,** 1189-200.
ROSENFIELD, A. & MAINE, D. 1985. MATERNAL MORTALITY-A NEGLECTED TRAGEDY: Where is the M in MCH? *The Lancet,* 326**,** 83-85.
ROTHWELL, P. M. 2005. External validity of randomised controlled trials: "To whom do the results of this trial apply?". *The Lancet,* 365**,** 82-93.
ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS 2012. Bacterial Sepsis in Pregnancy. *Green-top Guideline No. 64a.* Royal College of Obstetricians and Gynaecologists,.
RYAN, H. M., JONES, M. A., PAYNE, B. A., SHARMA, S., HUTFIELD, A. M., LEE, T., UKAH, U. V., WALLEY, K. R., MAGEE, L. A. & VON DADELSZEN, P. 2017. Validating the Performance of the Modified Early Obstetric Warning System Multivariable Model to Predict Maternal Intensive Care Unit Admission. *J Obstet Gynaecol Can,* 39**,** 728-733.e3.
RYMAN, T. K., ELSAYED, E. A., MUSTAFA, A. A., WIDOA, N. M., OMER, A. & KAMADJEU, R. 2011. Implementation of the reaching every district (RED) approach: experience from North Sudan. *East Mediterr Health J,* 17**,** 804-12.
SAY, L., CHOU, D., GEMMILL, A., TUNCALP, O., MOLLER, A. B., DANIELS, J., GULMEZOGLU, A. M., TEMMERMAN, M. & ALKEMA, L. 2014. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health.* England: 2014 World Health Organization.
SAY, L. & RAINE, R. 2007. A systematic review of inequalities in the use of maternal health care in developing countries: examining the scale of the problem and the importance of context. *Bull World Health Organ,* 85**,** 812-9.
SCHMIDT, P. E., MEREDITH, P., PRYTHERCH, D. R., WATSON, D., WATSON, V., KILLEN, R. M., GREENGROSS, P., MOHAMMED, M. A. & SMITH, G. B. 2015. Impact of introducing an electronic physiological surveillance system on hospital mortality. *BMJ Qual Saf,* 24**,** 10-20.
SCHNEIDER, H., OKELLO, D. & LEHMANN, U. 2016. The global pendulum swing towards community health workers in low- and middle-income countries: a scoping review of trends, geographical distribution and programmatic orientations, 2005 to 2014. *Hum Resour Health,* 14**,** 65.
SCHULZ, K. F., ALTMAN, D. G. & MOHER, D. 2010. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med,* 152.
SCOTT, C. A., BEWLEY, S., RUDD, A., SPARK, P., KURINCZUK, J. J., BROCKLEHURST, P. & KNIGHT, M. 2012. Incidence, risk factors, management, and outcomes of stroke in pregnancy. *Obstet Gynecol,* 120**,** 318-24.
SHAH, A., FAUNDES, A., MACHOKI, M., BATAGLIA, V., AMOKRANE, F., DONNER, A., MUGERWA, K., CARROLI, G., FAWOLE, B., LANGER, A., WOLOMBY, J. J., NARAVAEZ, A., NAFIOU, I., KUBLICKAS, M., VALLADARES, E., VELASCO, A., ZAVALETA, N., NEVES, I. & VILLAR, J. 2008. Methodological considerations in implementing the WHO Global Survey for Monitoring Maternal and Perinatal Health. *Bull World Health Organ,* 86**,** 126-31.
SHANKAR-HARI, M., PHILLIPS, G. S., LEVY, M. L., SEYMOUR, C. W., LIU, V. X., DEUTSCHMAN, C. S., ANGUS, D. C., RUBENFELD, G. D. & SINGER, M. 2016. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama,* 315**,** 775-87.
SHEIKH, S., QURESHI, R. N., KHOWAJA, A. R., SALAM, R., VIDLER, M., SAWCHUCK, D., VON DADELSZEN, P., ZAIDI, S. & BHUTTA, Z. 2016. Health care provider knowledge and routine management of pre-eclampsia in Pakistan. *Reprod Health,* 13**,** 104.
SHELDON, W. R., BLUM, J., VOGEL, J. P., SOUZA, J. P., GÜLMEZOGLU, A. M., WINIKOFF, B., ON BEHALF OF THE, W. H. O. M. S. O. M. & NEWBORN HEALTH RESEARCH, N. 2014. Postpartum haemorrhage management, risks, and maternal outcomes: findings

from the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG: An International Journal of Obstetrics & Gynaecology,* 121**,** 5-13.
SHENNAN, A. H., GREEN, M. & CHAPPELL, L. C. 2017. Maternal deaths in the UK: pre-eclampsia deaths are avoidable. *Lancet,* 389**,** 582-584.
SHIELDS, L. E., WIESNER, S., KLEIN, C., PELLETREAU, B. & HEDRIANA, H. L. 2016. Use of Maternal Early Warning Trigger tool reduces maternal morbidity. *Am J Obstet Gynecol,* 214**,** 527.e1-527.e6.
SINGER, M., DEUTSCHMAN, C. S., SEYMOUR, C. W., SHANKAR-HARI, M., ANNANE, D., BAUER, M., BELLOMO, R., BERNARD, G. R., CHICHE, J. D., COOPERSMITH, C. M., HOTCHKISS, R. S., LEVY, M. M., MARSHALL, J. C., MARTIN, G. S., OPAL, S. M., RUBENFELD, G. D., VAN DER POLL, T., VINCENT, J. L. & ANGUS, D. C. 2016. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama,* 315**,** 801-10.
SINGH, S., DOYLE, P., CAMPBELL, O. M., MATHEW, M. & MURTHY, G. V. S. 2016. Referrals between Public Sector Health Institutions for Women with Obstetric High Risk, Complications, or Emergencies in India – A Systematic Review. *PLOS ONE,* 11**,** e0159793.
SINGH, S., MCGLENNAN, A., ENGLAND, A. & SIMONS, R. 2012. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). *Anaesthesia,* 67**,** 12-8.
SITTIPARN, W. & SIWADUNE, T. 2017. Risk Score for Prediction of Postpartum Hemorrhages in Normal Labor at Chonburi Hospital. *J Med Assoc Thai,* 100**,** 382-8.
SMITH, G. B., ISAACS, R., ANDREWS, L., WEE, M. Y. K., VAN TEIJLINGEN, E., BICK, D. E. & HUNDLEY, V. 2017. Vital signs and other observations used to detect deterioration in pregnant women: an analysis of vital sign charts in consultant-led UK maternity units. *International Journal of Obstetric Anesthesia,* 30**,** 44-51.
SOHN, C. H., KIM, W. Y., KIM, S. R., SEO, D. W., RYOO, S. M., LEE, Y. S., LEE, J. H., OH, B. J., WON, H. S., SHIM, J. Y. & LIM, K. S. 2013. An increase in initial shock index is associated with the requirement for massive transfusion in emergency department patients with primary postpartum hemorrhage. *Shock,* 40**,** 101-5.
STARRS, A. M. 1997. *The Safe Motherhood Action Agenda: Priorities for the next decade* [Online]. Colombo, Sri Lanka. Available: http://documents.worldbank.org/curated/en/403701468764711167/pdf/multi-page.pdf [Accessed 27th November 2017].
STARRS, A. M. 2006. Safe motherhood initiative: 20 years and counting. *Lancet,* 368**,** 1130-2.
STELLENBERG, E. L. & NGWEKAZI, N. L. 2016. Knowledge of midwives about hypertensive disorders during pregnancy in primary healthcare. *Afr J Prim Health Care Fam Med,* 8**,** e1-6.
STETLER, C. B., DAMSCHRODER, L. J., HELFRICH, C. D. & HAGEDORN, H. J. 2011. A guide for applying a revised version of the PARIHS framework for implementation. *Implement Sci,* 6.
TEPOEL, M. R., SAFTLAS, A. F. & WALLIS, A. B. 2011. Association of seasonality with hypertension in pregnancy: a systematic review. *J Reprod Immunol,* 89**,** 140-52.
THADDEUS, S. & MAINE, D. 1994. Too far to walk: maternal mortality in context. *Social Science and Medicine,* 38**,** 1091-110.
THANGARATINAM, S., DATTA, A., ISMAIL, K. M. K. & KHAN, K. S. 2011a. What is the accuracy of blood pressure in predicting complications in pre-eclampsia? *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 96**,** Fa101.
THANGARATINAM, S., GALLOS, I. D., MEAH, N., USMAN, S., ISMAIL, K. M. & KHAN, K. S. 2011b. How accurate are maternal symptoms in predicting impending complications in women with preeclampsia? A systematic review and meta-analysis. *Acta Obstet Gynecol Scand,* 90**,** 564-73.
THE AMERICAN COLLEGE OF OBSTETICIANS AND GYNAECOLOGISTS 2013. Hypertension in Pregnancy. *In:* PREGNANCY, T. F. O. H. I. (ed.).
THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS 2002. Points to consider on multiplicity issues in clinical trials. *In:* PRODUCTS;, C. F. P. M. (ed.). Evaluation of Medicines for Human Use.
THE GAMBIA HEPATITIS STUDY GROUP 1987. The Gambia Hepatitis Intervention Study. *Cancer Research,* 47**,** 5782.
THE PARTNERSHIP FOR MATERNAL NEWBORN & CHILD HEALTH 2011. A Global Review of the Key Interventions Related to Reproductive, Maternal, Newborn and Child Health (RMNCH). . Geneva, Switzerland: PMNCH.

THE UK SEPSIS TRUST. 2017. *Inpatient Maternal Sepsis Tool* [Online]. United Kingdom: UK Sepsis Trust. Available: https://sepsistrust.org/wp-content/uploads/2017/08/Inpatient-maternal-NICE-Final-1107-2.pdf [Accessed 27th June 2018].

TONG, A., SAINSBURY, P. & CRAIG, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care,* 19**,** 349-357.

TORLONI, M. R., GOMES FREITAS, C., KARTOGLU, U. H., METIN GULMEZOGLU, A. & WIDMER, M. 2016. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. *Bjog,* 123**,** 2076-2086.

TOTEJA, G. S., SINGH, P., DHILLON, B. S., SAXENA, B. N., AHMED, F. U., SINGH, R. P., PRAKASH, B., VIJAYARAGHAVAN, K., SINGH, Y., RAUF, A., SARMA, U. C., GANDHI, S., BEHL, L., MUKHERJEE, K., SWAMI, S. S., MERU, V., CHANDRA, P., CHANDRAWATI & MOHAN, U. 2006. Prevalence of anemia among pregnant women and adolescent girls in 16 districts of India. *Food Nutr Bull,* 27**,** 311-5.

TRANQUILLI, A. L., DEKKER, G., MAGEE, L., ROBERTS, J., SIBAI, B. M., STEYN, W., ZEEMAN, G. G. & BROWN, M. A. 2014. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health,* 4**,** 97-104.

TREWEEK, S. & ZWARENSTEIN, M. 2009. Making trials matter: pragmatic and explanatory trials and the problem of applicability. *Trials,* 10**,** 37.

TSENG, J. & NUGENT, K. 2015. Utility of the Shock Index in Patients With Sepsis. *The American Journal of the Medical Sciences,* 349**,** 531-535.

TURAN, J., OJENGBEDE, O., FATHALLA, M., MOURAD-YOUSSIF, M., MORHASON-BELLO, I. O., NSIMA, D., MORRIS, J., BUTRICK, E., MARTIN, H., CAMLIN, C. & MILLER, S. 2011. Positive Effects of the Non-pneumatic Anti-shock Garment on Delays in Accessing Care for Postpartum and Postabortion Hemorrhage in Egypt and Nigeria. *Journal of Women's Health,* 20**,** 91-98.

UNFPA 2003. Making Safe Motherhood a Reality in West Africa. Using Indicators to Programme for Results. UNFPA: New York.

UNITED NATIONS 2015. The Millennium Development Goals Report 2015. Geneva: United Nations.

UNITED NATIONS COMMISSIONERS REPORT 2012. UN Commisssion on Life-Saving Commodities for women and children; Every women, every child.

UNITED NATIONS GENERAL ASSEMBLY. 2015. *Transforming our world: the 2030 Agenda for Sustainable Development 2015.* [Online]. United Nations. Available: https://sustainabledevelopment.un.org/content/documents/21252030%20Agenda%20for%20Sustainable%20Development%20web.pdf [Accessed 27th November 2017].

UNITED NATIONS INTER-AGENCY GROUP FOR CHILD MORTALITY ESTIMATION (UN IGME). 2017. *Levels and Trends in Child Mortality: Report 2017, Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation* [Online]. New York: United Nations Children's Fund. Available: https://www.unicef.org/publications/files/Child_Mortality_Report_2017.pdf [Accessed 04th December 2017].

UTZ, B., ASSARAG, B., ESSOLBI, A., BARKAT, A., EL ANSARI, N., FAKHIR, B., DELAMOU, A. & DE BROUWERE, V. 2017. Improving detection and initial management of gestational diabetes through the primary level of care in Morocco: protocol for a cluster randomized controlled trial. *Reproductive Health,* 14**,** 75.

VADER, J. P. 1998. Randomised controlled trials: A User's guide. *Bmj,* 317**,** 1258.

VAN DER GRAAF, R., KOFFIJBERG, H., GROBBEE, D. E., DE HOOP, E., MOONS, K. G. M., VAN THIEL, G. J. M. W., DE WIT, G. A. & VAN DELDEN, J. J. M. 2015. The ethics of cluster-randomized trials requires further evaluation: a refinement of the Ottawa Statement. *Journal of Clinical Epidemiology,* 68**,** 1108-1114.

VAN DER KOOI, T., SAX, H., PITTET, D., VAN DISSEL, J., VAN BENTHEM, B., WALDER, B., CARTIER, V., CLACK, L., DE GREEFF, S., WOLKEWITZ, M., HIEKE, S., BOSHUIZEN, H., VAN DE KASSTEELE, J., VAN DEN ABEELE, A., BOO, T. W., DIAB-ELSCHAHAWI, M., DUMPIS, U., GHITA, C., FITZGERALD, S., LEJKO, T., LELEU, K., MARTINEZ, M. P., PANIARA, O., PATYI, M., SCHAB, P., RAGLIO, A., SZILÁGYI, E., ZIĘTKIEWICZ, M., WU, A. W., GRUNDMANN, H. & ZINGG, W. 2018. Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections. *Intensive Care Medicine,* 44**,** 48-60.

VAN DILLEN, J., ZWART, J., SCHUTTE, J. & VAN ROOSMALEN, J. 2010. Maternal sepsis: epidemiology, etiology and outcome. *Curr Opin Infect Dis,* 23**,** 249-54.

VELAUTHAR, L., PLANA, M. N., KALIDINDI, M., ZAMORA, J., THILAGANATHAN, B., ILLANES, S. E., KHAN, K. S., AQUILINA, J. & THANGARATINAM, S. 2013. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55 974 women. *Ultrasound in Obstetrics & Gynecology,* 43**,** 500-507.

VICTORA, C. G., BLACK, R. E., BOERMA, J. T. & BRYCE, J. 2011. Measuring impact in the Millennium Development Goal era and beyond: a new approach to large-scale effectiveness evaluations. *The Lancet,* 377**,** 85-95.

VIGIL-DE GRACIA, P., ROJAS-SUAREZ, J., RAMOS, E., REYES, O., COLLANTES, J., QUINTERO, A., HUERTAS, E., CALLE, A., TURCIOS, E. & CHON, V. Y. 2015. Incidence of eclampsia with HELLP syndrome and associated mortality in Latin America. *Int J Gynaecol Obstet,* 129**,** 219-22.

VON DADELSZEN, P., PAYNE, B., LI, J., ANSERMINO, J. M., BROUGHTON PIPKIN, F., COTE, A. M., DOUGLAS, M. J., GRUSLIN, A., HUTCHEON, J. A., JOSEPH, K. S., KYLE, P. M., LEE, T., LOUGHNA, P., MENZIES, J. M., MERIALDI, M., MILLMAN, A. L., MOORE, M. P., MOUTQUIN, J. M., OUELLET, A. B., SMITH, G. N., WALKER, J. J., WALLEY, K. R., WALTERS, B. N., WIDMER, M., LEE, S. K., RUSSELL, J. A. & MAGEE, L. A. 2011. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet,* 377**,** 219-27.

VOUSDEN, N., LAWLEY, E., NATHAN, H. L., SEED, P. T., BROWN, A., MUCHENGWA, T., CHARANTIMATH, U., BELLAD, M., GIDIRI, M. F., GOUDAR, S., CHAPPELL, L. C., SANDALL, J. & SHENNAN, A. H. 2018. Evaluation of a novel vital sign device to reduce maternal mortality and morbidity in low-resource settings: a mixed method feasibility study for the CRADLE-3 trial. *BMC Pregnancy Childbirth,* 18**,** 115.

VOUSDEN, N., LAWLEY, E., NATHAN, L.H., SEED, P.T., GIDIRI, M.F., GOUDAR, S., SANDALL, J., CHAPPELL, L.C. & SHENNAN, A.H. ON BEHALF OF THE CRADLE TRIAL COLLABORATIVE GROUP 2019. Effect of a novel vital sign device on maternal mortality and morbidity in low-resource settings: a pragmatic, stepped-wedge, cluster-randomised controlled trial. *Lancet Global Health,* 7**,** e347-56.

W.K. KELLOGG FOUNDATION. 2004. *Logic Model Development Guide: Using logic models to bring together planning, evaluation and action* [Online]. Michigan. Available: https://www.wkkf.org/resource-directory/resource/2006/02/wk-kellogg-foundation-logic-model-development-guide [Accessed 20th November 2017].

WATERSTONE, M., BEWLEY, S. & WOLFE, C. 2001. Incidence and predictors of severe obstetric morbidity: case-control study. *Bmj,* 322**,** 1089-93; discussion 1093-4.

WEEKS, A. 2015. The prevention and treatment of postpartum haemorrhage: what do we know, and where do we go to next? *BJOG: An International Journal of Obstetrics & Gynaecology,* 122**,** 202-210.

WEKESAH, F. M., MBADA, C. E., MUULA, A. S., KABIRU, C. W., MUTHURI, S. K. & IZUGBARA, C. O. 2016. Effective non-drug interventions for improving outcomes and quality of maternal health care in sub-Saharan Africa: a systematic review. *Systematic Reviews,* 5**,** 137.

WELLS, K. B. 1999. Treatment research at the crossroads: the scientific interface of clinical trials and effectiveness research. *Am J Psychiatry,* 156**,** 5-10.

WEN, S. W., KRAMER, M. S., HOEY, J., HANLEY, J. A. & USHER, R. H. 1993. Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure. *J Clin Epidemiol,* 46**,** 1187-93.

WIDMER, M., PIAGGIO, G., NGUYEN, T. M. H., OSOTI, A., OWA, O. O., MISRA, S., COOMARASAMY, A., ABDEL-ALEEM, H., MALLAPUR, A. A., QURESHI, Z., LUMBIGANON, P., PATEL, A. B., CARROLI, G., FAWOLE, B., GOUDAR, S. S., PUJAR, Y. V., NEILSON, J., HOFMEYR, G. J., SU, L. L., FERREIRA DE CARVALHO, J., PANDEY, U., MUGERWA, K., SHIRAGUR, S. S., BYAMUGISHA, J., GIORDANO, D. & GÜLMEZOGLU, A. M. 2018. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. *New England Journal of Medicine*.

WILSON, M. G., BASTA, T. B., BYNUM, B. H., DEJOY, D. M., VANDENBERG, R. J. & DISHMAN, R. K. 2010. Do intervention fidelity and dose influence outcomes? Results from the move to improve worksite physical activity program. *Health Educ Res,* 25**,** 294-305.

WIRA, C. R., FRANCIS, M. W., BHAT, S., EHRMAN, R., CONNER, D. & SIEGEL, M. 2014. The shock index as a predictor of vasopressor use in emergency department patients with severe sepsis. *West J Emerg Med,* 15**,** 60-6.

WOMAN TRIAL COLLABORATORS 2017. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage

(WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet,* 389**,** 2105-2116.
WORLD HEALTH ORGANISATION 1997. The sisterhood method for estimating maternal mortality: Guidance notes for potential users. *In:* WORLD HEALTH ORGANISATION (ed.). Geneva, Switzerland.
WORLD HEALTH ORGANISATION. 2005a. *Health and the Millenium Development Goals* [Online]. Geneva Switzerland. Available: http://www.who.int/hdp/publications/mdg_en.pdf [Accessed 27th November 2017].
WORLD HEALTH ORGANISATION 2005b. The World Health Report 2005 - make every mother and child count. Geneva, Switzerland.
WORLD HEALTH ORGANISATION 2006. World Health Report 2006: working together for health. Geneva, Switzerland: World Health Organisation,.
WORLD HEALTH ORGANISATION. 2007. *Maternal Mortality in 2005: estimates developed by WHO, UNICEF, UNFPA and the World Bank* [Online]. World Health Organisation, Geneva, Switzerland. Available: http://www.who.int/whosis/mme_2005.pdf [Accessed 20th November 2017].
WORLD HEALTH ORGANISATION. 2010. *International Statistical Classification of Diseases and Related Health Problems* [Online]. World Health Organisation. Available: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf [Accessed 20th November 2017].
WORLD HEALTH ORGANISATION. 2011. *WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia* [Online]. Geneva, Switzerland: World Health Organisation. Available: http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf [Accessed 3rd April 2017].
WORLD HEALTH ORGANISATION. 2012a. *The WHO application of ICD-10 to deaths during pregnancy, childbirth and puerperium: ICD MM.* [Online]. Geneva, Switzerland. Available: http://apps.who.int/iris/bitstream/10665/70929/1/9789241548458_eng.pdf?ua=1 [Accessed 18th January 2018].
WORLD HEALTH ORGANISATION. 2012b. *WHO recommendations for the prevention and treatment of postpartum haemorrhage* [Online]. Geneva, Switzerland: World Health Organisation. Available: http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf [Accessed 30th October 2017].
WORLD HEALTH ORGANISATION. 2015a. *Strategies Toward Ending Preventable Maternal Mortality (EPMM)* [Online]. Geneva, Switzerland. Available: http://www.everywomaneverychild.org/images/EPMM_final_report_2015.pdf [Accessed 28/11/2017 2017].
WORLD HEALTH ORGANISATION. 2015b. *Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division* [Online]. Geneva, World Health Organisation. Available: http://apps.who.int/iris/bitstream/10665/194254/1/9789241565141_eng.pdf?ua=1 [Accessed].
WORLD HEALTH ORGANISATION. 2015c. *WHO recommendations for the prevention and treatment of maternal peripartum infections* [Online]. World Health Organization, Geneva. Available: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/peripartum-infections-guidelines [Accessed 27th June 2018].
WORLD HEALTH ORGANISATION. 2016. *WHO recommendations on antenatal care for a positive pregnancy experience* [Online]. Geneva, Switzerland. Available: www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/ [Accessed 22nd August 2018].
WORLD HEALTH ORGANISATION. 2017a. *Statement on Maternal Sepsis* [Online]. Geneva, Switzerland World Heath Organisaion,. [Accessed 26th June 2018].
WORLD HEALTH ORGANISATION 2017b. WHO Model List of Essential Medicines. World Health Organisaion, Geneva, Switzerland.
YUSSOF, S. J., ZAKARIA, M. I., MOHAMED, F. L., BUJANG, M. A., LAKSHMANAN, S. & ASAARI, A. H. 2012. Value of Shock Index in prognosticating the short-term outcome of death for patients presenting with severe sepsis and septic shock in the emergency department. *Med J Malaysia,* 67**,** 406-11.
ZIRABA, A. K., MILLS, S., MADISE, N., SALIKU, T. & FOTSO, J. C. 2009. The state of emergency obstetric care services in Nairobi informal settlements and environs: results from a maternity health facility survey. *BMC Health Serv Res,* 9**,** 46.

7 Appendix

7.1 Trial Clusters

Cluster Primary Investigator and Affiliation	Tertiary Facilities	Secondary Facilities	Primary Facilities
Adrian Brown, Maternity Worldwide, UK	St Paul's Hospital, Addis Ababa, Ethiopia	Ras Desta, Addis Ababa, Ethiopia	Selam Health Center (Woreda 9), Woreda 7 Health Centre (Gulele)/Hidasse, Woreda 10 Health Center, (Gulele)/shegole, Free Methodist Health Center, Woreda 5 Health Center, Woreda 2 Health Center Michewe, Addis Ketema Health Center, Woreda 5/18 Health Center (Addis Ketema), Woreda 7 Health Center (Addis Ketema), Woreda 7 Health Center (Addis Ketema), Woreda 10 Addis Ketema, Woreda 5 Abebe Bikila, Ras Emiru Health center, Gulele Semen, Simgn Kebede, Kolfe Woreda 2, Addis Gebeya HC, Mikililand Health Centre
Francis Gidiri, University of Zimbabwe, Zimbabwe	Mbuya Nehanda Maternity Hospital, Harare, Zimbabwe	Concession District Hospital Makumbi Hospital	Henderson Clinic, Christon Bank Clinic, Nyabira Clinic, Gwebi College Cllnic, Mount Hampden Clinic, Dzivarasekwa Extension Clinic, St Joseph's Clinic, Mabvuku Polyclinic, Warren Park Polyclinic, Hatcliff Polyclinic, Rujeko Polyclinic, Parirenyatwa City clinic, Tafara Clinic, Greendale Clinic, Eastlea Clinic, Highlands Clinic, Borrowdale Clinic, Mt Pleasant Clinic, Avondale Clinic, Belvedere Clinic, Mabelreign Clinic, Malborough Clinic
Sebastian Chinkoyo, Ndola Teaching Hopital, Ndola, Zambia	Ndola Teaching Hospital	N/A	Chipokota Mayamba Clinic, Chipulukusu Clinic, Commando Camp Clinic, Dola Hill Clinic, Itawa Clinic, Kabushi Clinic, Kalewa Clinic, Kaloko Clinic, Kaniki Clinic, Kawama Clinic, Lubuto Clinic, Main Masala Clinic, Mushili Clinic, Ndeke Clinic, New Masala Clinic, Nkwazi Clinic, Padmodzi Clinic, Peter Singogo Clinic, Prisons Clinic, Railway Surgery, St Dominic Mission Hospital, Tug Argan Clinic, Twapia Clinic

Matthew Clarke, Welbodi Partnership, Freetown, Sierra Leone	Princess Christian Maternity Hospital, Freetown, Sierra Leone	Rokupa Government Hospital	Approve School CHC, Haja Neneh, Jenner Wright CHC, Kissy CHC, Konkay CHC, Kuntorloh CHC, Looking Town MCHP, Moyiba CHC, Principal Medical Officer Clinic, Ross Road CHC, St. Joseph CHC
Carwyn Hill, Hope Health Action, Cap Haiten Haiti	Fort Saint Michel Hopital Convention Baptiste d'Haiti Justinian University Hospital	Centre de Sante Quartier-Morin	Centre de Sante de Cadush, Centre de Sante de Morne Pele, Centre de Sante Labadie, Centre de Sante Limonade, Centre de Sante Porte Ouverte, Centre de Sante St Charles, Dispansaire St. Louis, Dispensaire de Grand Pre, Unite de Lutte pour la Sante (ULS), Centre de Sante de Madeline
Mrutyunjaya Bellad, Jawarharlal Nehru Medical College, KLE University, Belgaum, India		Al Shifa Hospital, Arogya hospital Mudalgi, Arogya woman child Hospital, Mahila and Childrens Hospital Dhondiba Jadhav Memorial Hospital, Dr Kattimani Hospital, Ganga surgical and Maternity Clinic, Gokak General Hospital, Gourishankar Hospital Gokak J G Cooperative Hospital, Jayaratna Hospital, Kadagalikar Maternity and Children Hospital, Kappalaguddi Hospital, KHI Hospital. Masurkar	Akkatangerhal SC Dasanatti, Akkatangerhal (PHC+ Sub Centres AK Hal I & II, Akkatangerhal SC Iranatti, Akkatangerhal SC Panjanatti, Ankalagi (PHC+ Sub Centres I and II), Ankalagi SC Gujanal, Ankalagi SC Mallapur, Ankalagi SC Suladal, Bairanatti (PHC+ Sub Centres I), Bairanatti SC Sunadholi, Bairanatti SC Tigadi, Balobal SC Hunshyal, Balobal SC Sangankeri, Balobal (PHC and SC I), Balobal SC Arabhavi, Balobal SC Lolasur, Betageri SC Chikkanandi, Betageri (PHC and SC I), Company Hospital Gokak Falls, Hallur (PHC and SCI and II), Hallur SC Khanatti, Kallolli (PHC and SC I, II), Khanagaon (PHC and SCI), Khanagaon SC DG Hatti, Khanagaon SC Shiltibhavi, Konnur (PHC SC I and II), Konnur SC Godachinamalki, Konnur SC Gokak Falls i and II, Konnur SC Melamatti, Konnur SC Nandagaon, Koujalagi (PHC and SC I and II), Koujalagi SC Kalliguddi, Kulagod (PHC SC I and II), Kulagod SC Dhavaleshwar, Mamadapur (PHC and SCI), Mamadapur SC Maradishivapur, Masaguppi (PHC SCI), Masaguppi SC Dharmatti, Masaguppi SC Vadratti, Melavanki PHC (PHC+ SC-1), Melavanki PHC -SC Maladinni, Melavanki PHC -SC Upparatti, Naganur (PHC SCI), Naganur SC Gurlapur, Naganur SC Mudalagi I and II, Sindhikurabet (PHC SC I and II), Sindhikurabet

		Hospital, Mudalagi CHC, Muragod Hospital, Navajeevan Maternity & Nursing Home, Nayakwadi Hospital, Shanta Nursing and Maternity Home, Soubhagya Nursing and Maternity Home	Ghataprabha I and II, Sindhikurabet SC Dupdhal, Sindhikurabet SC Duradundi, Talakatnal (PHC and SC), Talakatnal SC Gosabal, Talakatnal SC Uddagatti, Tavag (PHC SC I and II), Tavag SC Benachinamardi, Tavag SC Kolavi, Tavag SC Urabinatti, Tukkanatti (PHC SC), Tukkanatti SC PG Mallapur, Tukkanatti SC Rajapur, Yadawad (PHC and SC), Yadawad SC Avaradi, Yadawad SC Girisagar, Yadawad SC Yaragudri
Josephat Byamugisha, Makere University, Kampala, Uganda	Mulago and Kawempe Hospital	Lubaga Hospital, Mengo Hospital, Nsambya Hospital	Kawala Health Centre III, Kisenyi Health Centre, Kisugu Health Centre III, Kiswa Heaslth Centre III, Kitebi Health Centre III, Komamboga Health Centre III, Naguru general hospital, Naguru Teenage Centre, Kibuli Hospital
Bellington Vwalika, University of Zambia, Lusaka, Zamba	University Teaching Hospital	Chainama, Chainda, Chawama, Kalingalinga, Kanyama, Mtendere, Chilenje, Chipata, Levy Hospital, Matero Referral, Sikanze	Bauleni, Chaisa, Chazanga, Chelstone, Civic Center, George, Kabwata, Kamwala, Kaunda Square, Matero Main, Ngombe, Prisons, Railway, State House, State Lodge
Grace Makonyola, Maternity Worldwide, Malawi	Zomba central Hospital	Balaka, Holy Family, Machinga, Mangochi, St Lukes, Pirimiti	Chingale, Chipini, Magomero, Matawale, Matiya, Mayaka Namikango , Ntaja, Phalombe
Julius Wandabwa, Sanyu Africa Research Institute, Mbale, Uganda		Mbale regional referral hospital	Ahamadiya. Atuturi hospital, Bubulo, Budadiri, Budaka Bududa hospital, Bufumbo, Bugobero, Bukedea, Bukiende, Bumadanda, Bumasike, Bunampogo, Bungokho, Busano, Bushikori, Busiu, Busolwe Hospital, Buwangwa, Kadama, Kamonkoli, Kibuku, Kolonyi, Lwangoli, Makhonje, Maluku, Mbale prisons, Mt.elgon hospital, Naiku, Nakaloke, Namakwekwe, Namanyonyi, Namatala, Namawanga, Pallisa hospital, Police 2, Siira HCIII, Sironko, Tirinyi, Wanale

7.2 Training Materials

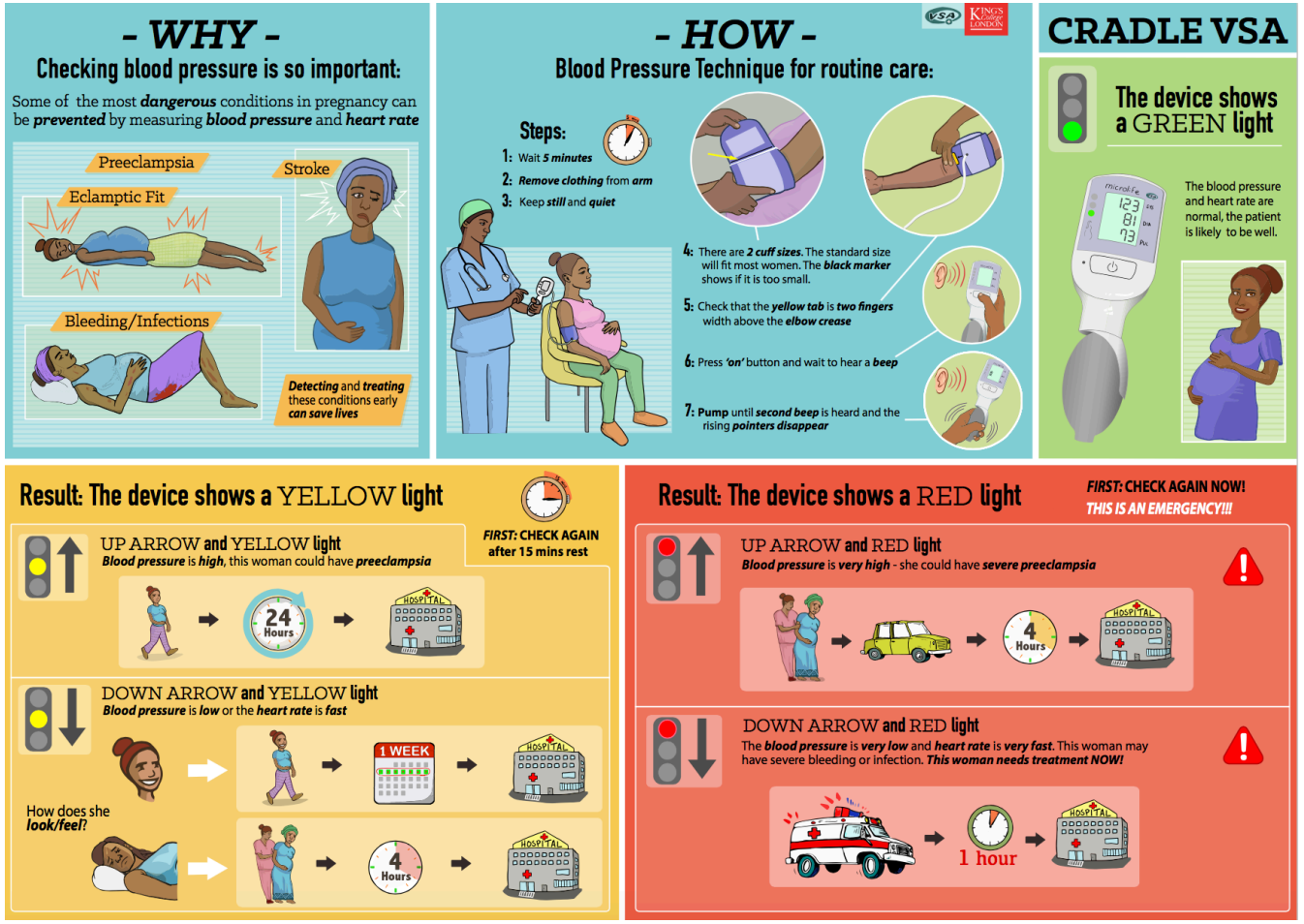


Figure 31 Poster for health care providers without formal training

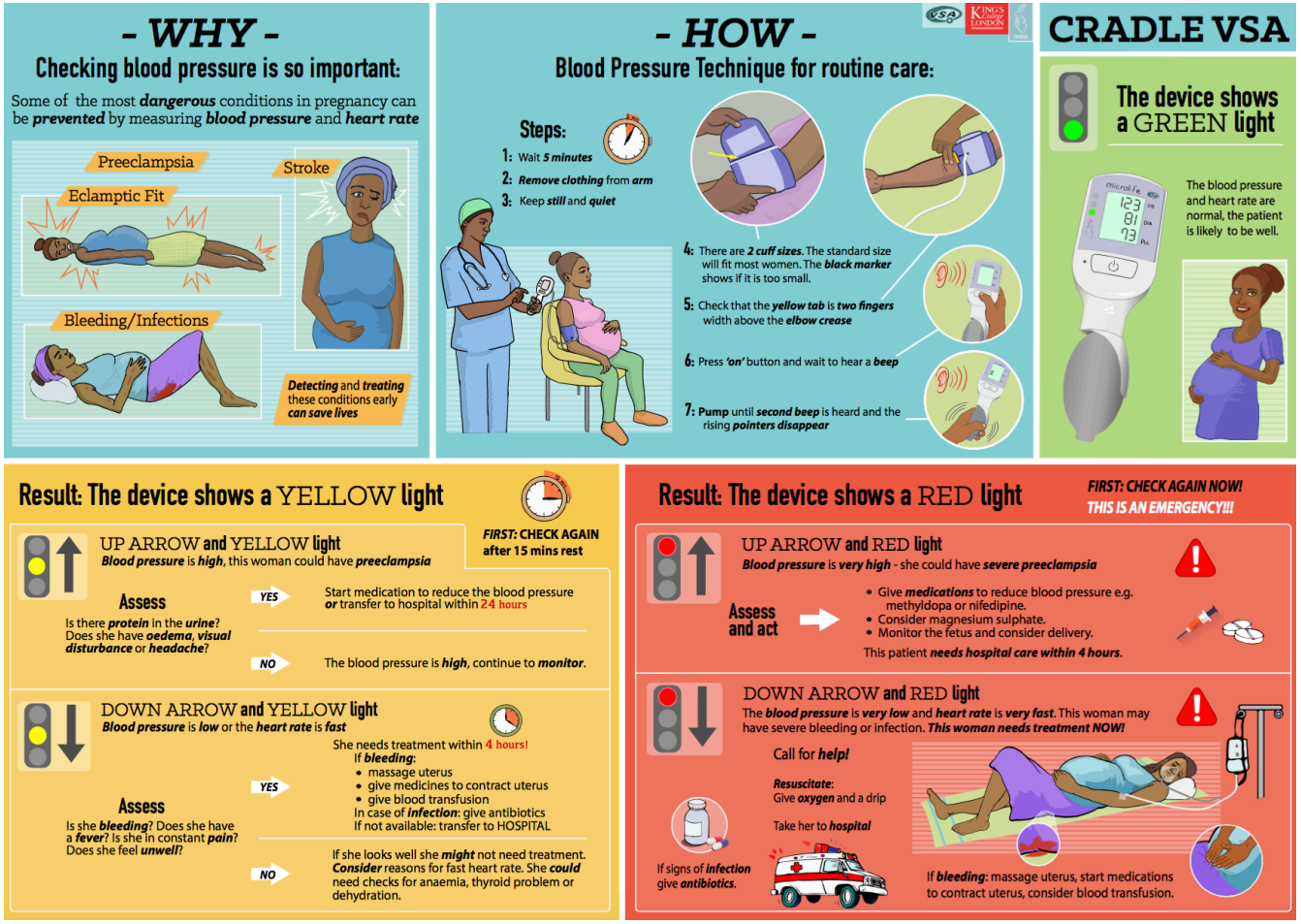


Figure 32 Poster for trained health care providers

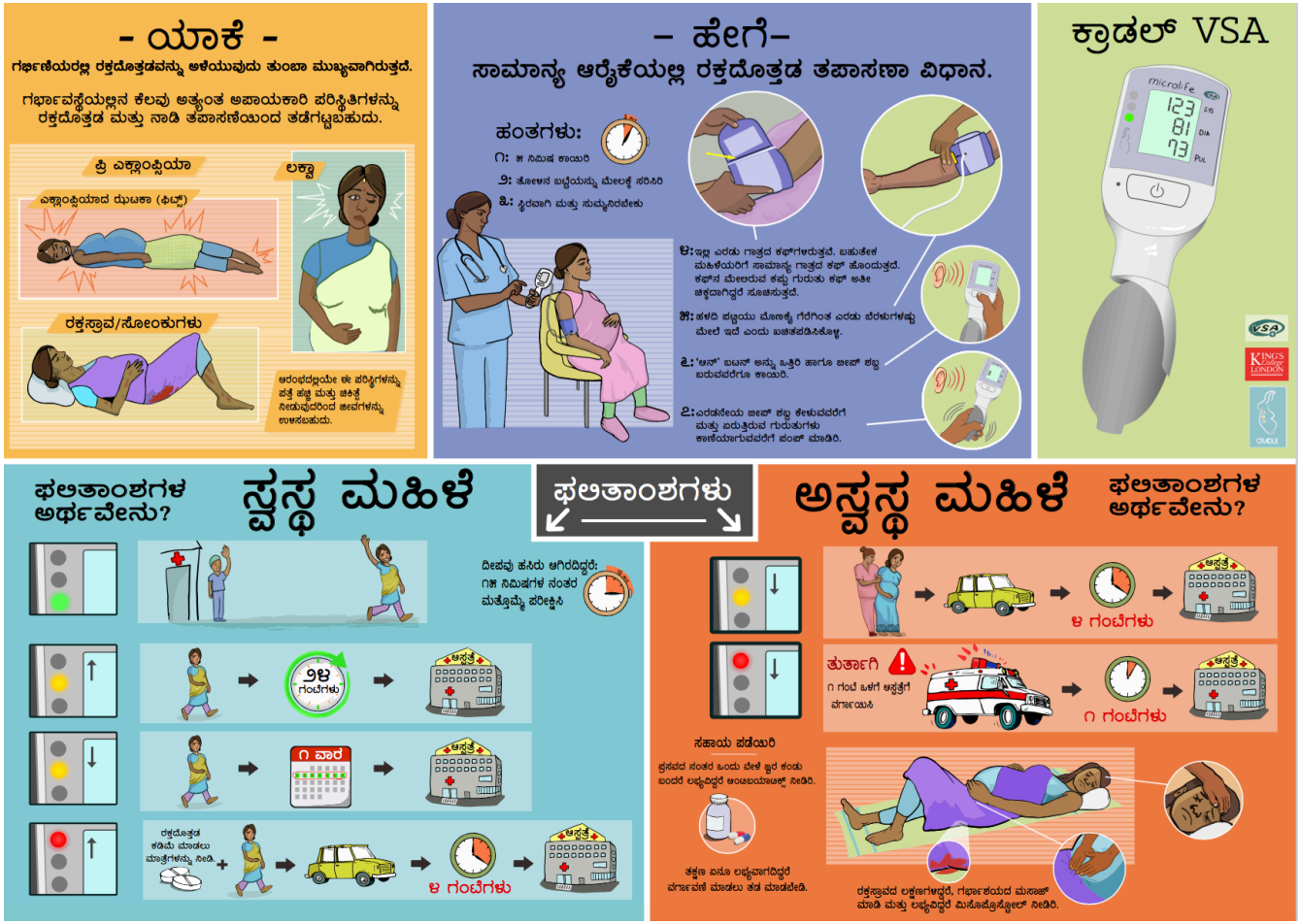


Figure 33 Cultural adaptation of poster and translation into Kannada

CRADLE 3
User Manual

Table of Contents

Overview 1

a) Purpose of this training module

This module is a training document that aims to train health providers to correctly use the CRADLE Vital Sign Alert and improve measurement of blood pressure (BP) and pulse.

b) Who should participate in training to use the CRADLE VSA?

The guide is intended primarily for trainers who will train healthcare providers who regularly measure vital signs, supervisors, and managers of health centres and hospitals to use the CRADLE VSA.

c) Objectives

At the end of the session, participants will be able to:

- Describe errors when measuring BP
- Describe how to reduce errors when measuring BP
- Correctly use the CRADLE VSA
- Correctly carry-out BP and pulse measurement using the CRADLE VSA
- Describe how to respond to error messages of the CRADLE VSA
- Describe how to care for and maintain the CRADLE VSA
- Identify abnormal BP and shock
- Interpret flashing traffic lights and arrows
- Describe clinical response to flashing traffic lights

d) Facilitator preparation prior to conducting the training activity:

- Review the training module and materials.

- Collect documents for distribution to the participants and print evaluation materials:

- Posters
- Training Register

- BP usually decreases during the 2nd trimester but may return to pre-pregnancy level or above pre-pregnancy level in the 3rd trimester
- BP should be checked:
    - Routinely during antenatal visits and while monitoring during labor/after delivery
    - Any time a pregnant woman presents with a problem or emergency
    - Any time a woman after delivery presents with a problem or emergency
- Having an accurate BP measurement is important because:
    - The misdiagnosis of high BP will lead to unnecessary treatment
    - The misdiagnosis of normal BP in women with high or low BP could lead to tragic consequences if necessary treatment and follow-up are not provided
- BP readings are prone to inaccuracy due to:
    - Observer error e.g. not correctly identifying Korotkoff sounds when listening with a stethoscope
    - Methodology error e.g. choosing the wrong size cuff
    - Inaccurate devices
    - Rise in BP caused by anxiety/fear due to the effects of attendance at the clinic.

a) Best practice for blood pressure measurement

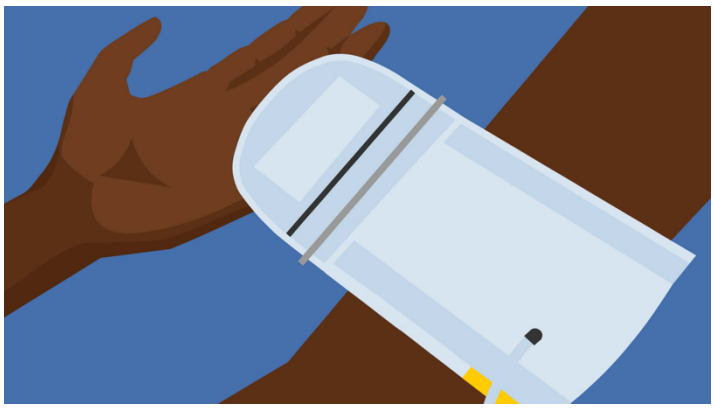
- Before taking the blood pressure, the patient should remain seated and at rest for 5 minutes

- Ensure the patient is seated with feet on the floor. If this isn't possible they should lie on their left side and check the BP in left arm.
- Support the arm on a table/cushion or by their side. The arm should be at the level of the heart.
- Explain the procedure and gain permission
- Remove all tight clothes from around the arm.
- Explain what the patient will experience:
    - Tight feeling, Minor discomfort perhaps, Pins and needles in fingers
- Ask her not to talk during the measurement.

b) Common Errors

1. Wrong size cuff:

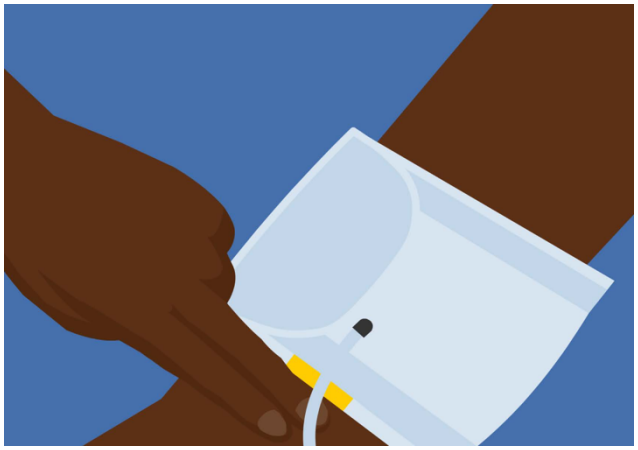
- There are two cuff sizes for the device, standard or large.
- The standard cuff will fit most women (arm circumference 22cm-32cm).
- When you fit the cuff the metal bar should the cross the black marker.
- If it does not then the cuff is too small, change to the large cuff (arm circumference 32cm – 42cm)



2. Wrong position of the cuff:

- The Velcro should be tightened so that the cuff is secure on the arm- but not tight.

- You should be able to insert two fingers between the cuff and the arm.
- The yellow tab should be two fingers width above the elbow crease.



3. Wrong patient position:

- Blood pressure should always be checked in the sitting position.
- Her legs should not be dangling or crossed. Her feet should be supported or on the ground
- If the patient cannot sit up, lie her on her left side and make sure to document this. Check BP in the inferior arm.
- If the patient cannot turn on her side, place a wedge under her right hip. Check BP in the inferior arm.

Using the CRADLE VSA

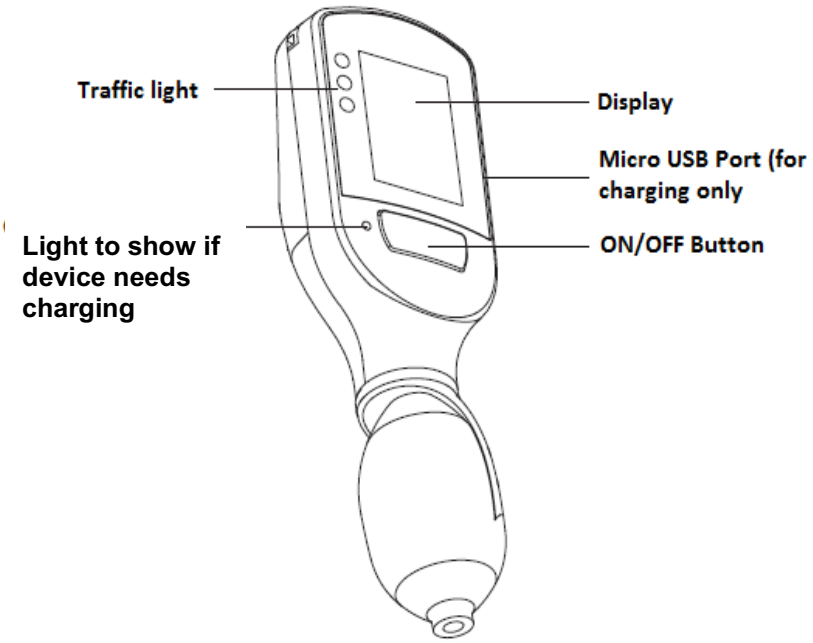
3

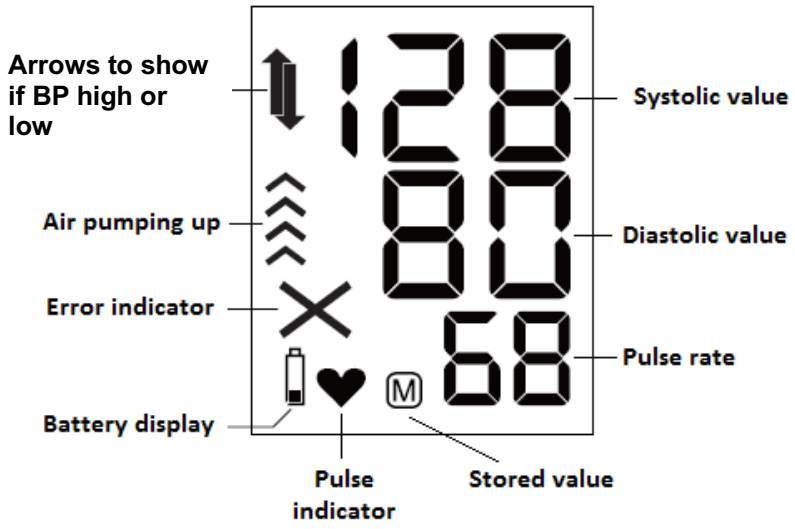
- The intended use of the Microlife VSA is a non-invasive digital BP monitor using oscillometric technique and an upper-arm BP cuff to measure systolic and diastolic blood pressures according to Korotkoff Phase I (for sBP) and V (for dBP). The device also incorporates an algorithm for the detection of hypovolemic shock.

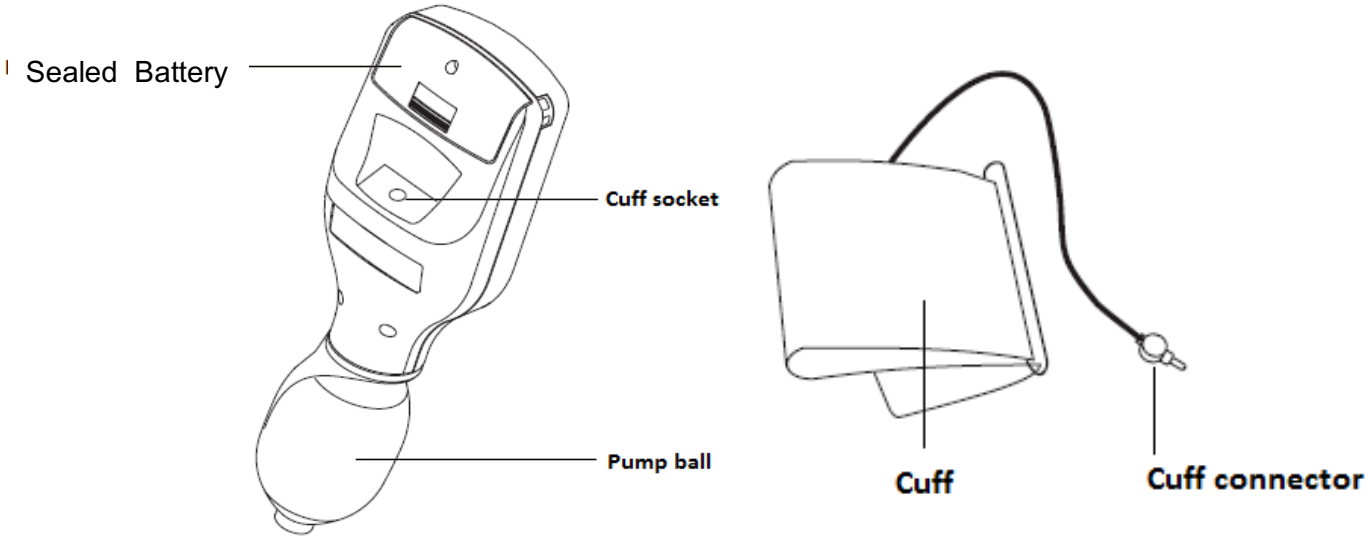
- The VSA can accurately measure BP in pregnant patients including those with known or suspected pre-eclampsia. It combines the advantages of an automatic BP monitor and auscultatory sphygmomanometer designed to provide convenient, accurate and reliable BP measurements according to guidelines of the British Hypertension Society and World Health Organization.

- The VSA has been validated for pregnant women as well as non-pregnant adults.

a) Features of the device

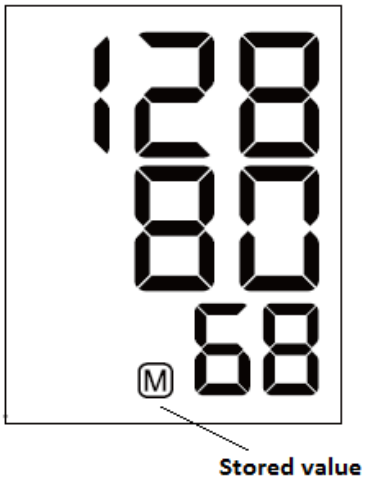




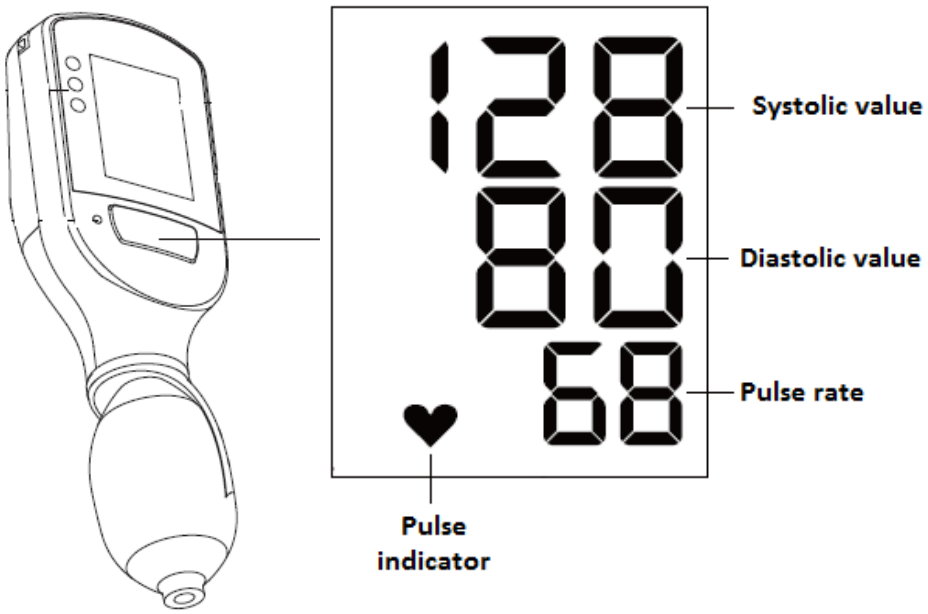


b) Memory

- The device automatically stores the last reading
- To show the stored reading:
- Hold down the ON/OFF button (the instrument must have been switched off beforehand) until memory appears and then release the button.



c) Use of the device



- Fit the cuff to the patients arm as described above
- Ensure the cuff is plugged in to the device
- Turn the device on as demonstrated above
- Pump approximately 40 mmHg higher than the expected systolic blood pressure value.
- A beep will sound and flashing arrows will disappear when you have reached the appropriate pressure, this will be at a number over 180.

- NOTE: If you have not pumped enough, the following rising pointers will appear again and flash telling you to pump higher.

If this occurs, continue pumping up the cuff until this sign disappears.

- After pumping, the measurement is taken automatically and will be shown on the screen.
- Ask the patient to relax, not to move and not to tense their arm muscles until the measurement result is displayed.

- The patient should breathe normally and not talk.
- During the measurement, the pulse indicator flashes on the display and a beep sounds every time a heartbeat is detected.
- The result, comprising the systolic and the diastolic blood pressure value and the pulse rate is displayed and a longer beep sound is heard.

d) Error Messages

- If an error occurs during the measurement, the measurement is interrupted, and an error message is displayed.
- Check the cuff is in the correct position, it is attached correctly to the device and that the patient is still and quiet.
- Then try again.

Error	Description	Potential cause and remedy
«X 1»	Signal too weak	The pulse signals on the cuff are too weak. Re-position the cuff and repeat the measurement.*
«X 2»	Error signal	During the measurement, error signals were detected by the cuff, caused for instance by movement or muscle tension. Repeat the measurement, keeping your arm still.
«X 3»	No pressure in the cuff	An adequate pressure cannot be generated in the cuff. A leak may have occurred. Check that the cuff is correctly connected and is not too loose. Repeat the measurement.
«X 5»	Invalid result	The measuring signals are invalid and no result can therefore be displayed. Read through the checklist for performing reliable measurements and then repeat the measurement.*
«HI»	Pulse or cuff pressure too high	The pressure in the cuff is too high (over 300 mmHg) OR the pulse is too high (over 200 beats per minute). Relax and repeat the measurement.*
«LO»	Pulse too low	The pulse is too low (less than 40 beats per minute). Repeat the measurement.*

Identifying abnormal vital signs and the clinical response

4

- The CRADLE VSA measures blood pressure and heart rate, and automatically calculates the shock index.
- When measurement is complete, you will see a traffic light. These lights indicate whether the results are within normal limits or higher/lower than normal.
- If they are higher or lower than normal you will see either an “Up arrow” (↑) or “Down arrow” (↓)
- It is important that everyone understands both the lights and the arrows when deciding how to manage patients.
- SI is a calculation of HR divided by Systolic Blood Pressure.
- It is the best vital sign for prediction of maternal severe morbidity such as significant blood transfusion or admission to higher level care facility.
- If the results show red repeat the reading again immediately.
- If the results show yellow repeat again in 15 minutes of rest.
- If yellow or red light shows once only, measure vital signs a third time and follow pathway of most consistent light (i.e. if results show yellow then green, check a third time, if the third result is yellow then act on this as it is the most common result)

Table 1. Classification of High blood pressure and CRADLE VSA RESULTS				
Category	Systolic BP (mmHg)		Diastolic BP (mmHg)	Light and Arrow Results
Severe hypertension	≥ 160	and / or	≥ 110	RED LIGHT UP ARROW
Hypertension	≥ 140 & ≤ 159	and / or	≥ 90 & ≤ 109	YELLOW LIGHT UP ARROW
Normal	< 140	and	< 90	GREEN LIGHT
Borderline low BP	≤ 100 & > 90			
Very low BP	≤ 90 & > 60			
Extremely low BP	≤ 60			

Table 2. Shock Index (SI)*		
Category	Shock Index (HR / sBP)	Light and Arrow Results
Severe shock	≥ 1.7	RED LIGHT DOWN ARROW
Shock	≥ 0.9 and <1.7	YELLOW LIGHT DOWN ARROW
Normal	< 0.9	GREEN LIGHT

a) Green light:

- BP <140 systolic and <90 diastolic *and* shock index <0.9.
- The woman is likely to be healthy
- Continue with normal care

b) Yellow light and up arrow:

- Systolic BP ≥140 & ≤159 and/or diastolic ≥90 & ≤109
- This is raised BP this patient may have preeclampsia. Action is needed
- Manage as you would normally e.g. measure urine dipstick, check for signs and symptoms (e.g. headaches, visual disturbance) and act accordingly
- If in the community transfer when practical (preferably within 24 hours)

c) Yellow light and down arrow:

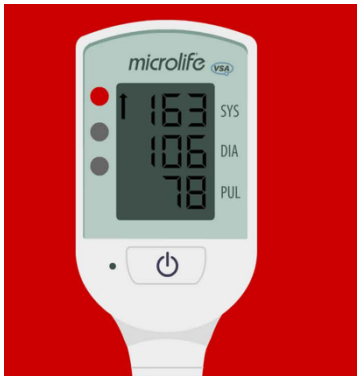
- Shock Index (HR/Systolic BP) is ≥0.9 and <1.7
- This result can be common in pregnant women, however;
- It may indicate that the mother is developing infection or bleeding. The patient needs to be assessed to decide what action is required.

- If she is well (no bleeding, no signs of infection, feels well) she may have anaemia, dehydration, an irregular heart rhythm or endocrine disease or her blood pressure may be low in pregnancy. Consider undertaking routine checks for these when possible.

- If she is unwell e.g. vaginal bleeding, fever, discharge, constant abdominal pain or if she feels unwell e.g. feverish, pale, sweaty, breathless
    - Resuscitate as necessary e.g. keep warm, elevate legs.
    - Transfer urgently (preferably within 4 hours).

- If bleeding, uterine massage after delivery of placenta, control of bleeding e.g. misoprostol, oxytocin, depending on what's available
- If sepsis, consider starting antibiotics if available.

d) Red light and up arrow:



- Systolic ≥160 and/or diastolic ≥110
- This is very raised BP and indicates urgent action is needed
- Manage as you would normally e.g. measure urine dipstick, check for signs and symptoms and act accordingly
- Give antihypertensives if available e.g. methyldopa, nifedipine, labetalol
- Consider magnesium sulfate (intramuscular) if available
- If in the community transfer as soon as possible (preferably within 4 hours)
- Monitor the baby.
- If BP remains uncontrolled and gestation appropriate, seek senior advice regarding need to deliver.

e) Red light and down arrow:

- Shock Index (HR/Systolic BP) is ≥ 1.7
- This may indicate serious infection or bleeding, urgent action is needed
- In community or hospital:

Stay calm. Do NOT leave the woman alone.

Get HELP

Assess the mother

Is she pale, sweaty, cold, breathing fast, drowsy or confused?

Is she unwell e.g. vaginal bleeding, fever, discharge, constant pain?

Keep her warm and elevate legs if possible

- In community:

Organise immediate transfer (within 1 hour)

If bleeding, uterine massage after delivery of placenta, give medication to contract uterus if available e.g. misoprostol 600mcg orally.

If sepsis, consider starting antibiotics

- In hospital:

Oxygen

IV fluids give quickly through a large bore cannula e.g. 2 litres in first hour

Collect blood to test haemoglobin; do an immediate cross-match

Catheterise the bladder to monitor input/output

Decide on the cause of shock and manage as you would normally

If bleeding transfuse blood, give uterotonics such as IV oxytocin, misoprostol or carboprost

Consider operative interventions if appropriate and available

If severe infection, keep hydrated, give IV antibiotics

Care and maintenance of the CRADLE VSA

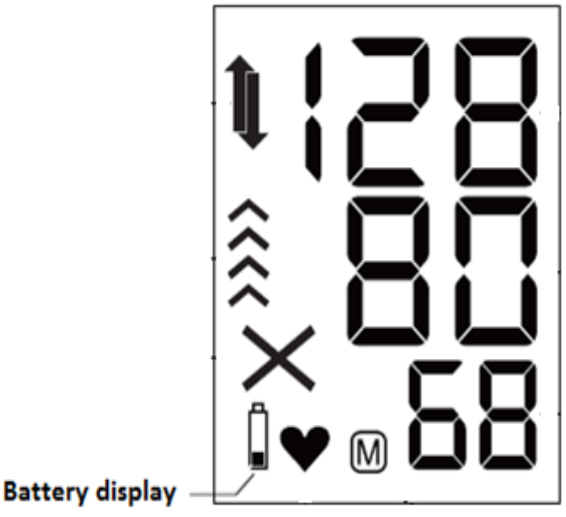
4

a) Cleaning CRADLE VSA

- Clean the device only with a soft, dry cloth.
- Cleaning the cuff:
  - Take out the bladder.
  - Fold and place the cuff cover inside a washing bag.
  - Wash the cuff cover with warm water and a mild detergent in a washing machine.
  - Air dry the cuff. DO NOT iron the cuff cover.

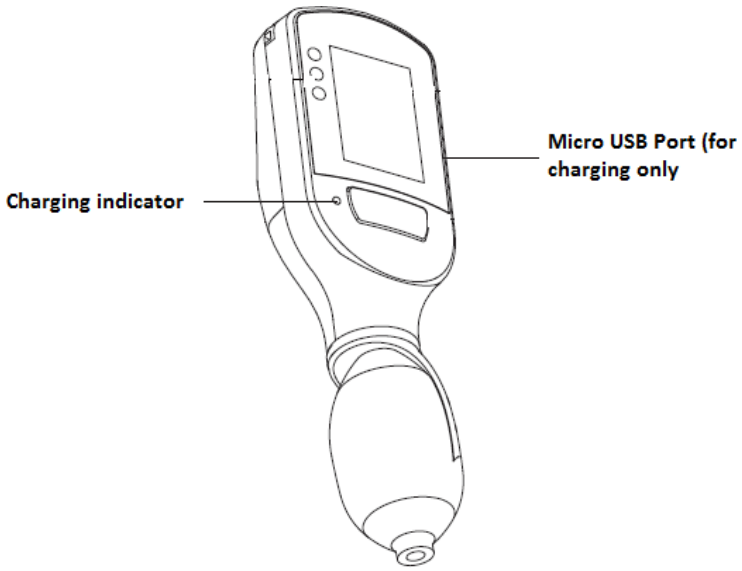
b) Charging VSA

- If the batteries are almost empty, the battery display will flash and a partly filled battery is displayed. The device will still work reliably but it should be charged
- If the batteries are flat, the battery display will flash, and a flat battery is displayed. The device will not work until charged



- The battery will last for 200 measurements.

- Depending how often the devices will be used in your area they will need charging at least once a week.
- The manager of each area should allocate a person to be responsible for this task and a safe designated place for the devices to be charged and stored.
- To charge the device connect it to the mains electricity using the charger or to a computer using the USB cable.
- During the charging process, the charging indicator will light up in orange.
- When the battery is completely charged, the charging indicator will light up in green.
- The device cannot be used while it is being charged.
- To improve the battery life of the device, charge the batteries until the charging indicator turns to green before using the machine for the first time and do not let the battery run down completely.



c) Security and Care of Devices

- The manager of each area should allocate a safe designated place for the devices to be stored when not in use.
- Devices are portable and where possible should be attached to firmer objects such as trolleys or tables using the cable wire and ferrules provided.
- Never attempt to open the devices, keep them out of direct sunlight and away from moisture.

CRADLE 3 Training Guide

TABLE OF CONTENTS **PAGE NUMBERS**

1. Trial Synopsis

Title of Clinical Trial	CRADLE 3 (Community Blood Pressure Measurement in Rural Africa and Asia: The Detection of Underlying Pre-eclampsia and Shock) Stepped-Wedge Randomised Control Trial
Protocol Acronym	CRADLE 3
Sponsor Name	King's College London
Chief Investigator	Professor Andrew Shenna
REC number	LRS-14/15-1484
Purpose of the trial	To determine whether implementation of the CRADLE VSA device and simple training package into community and facility care will reduce maternal mortality and major morbidity from the three leading causes of maternal death worldwide (obstetric haemorrhage, sepsis and pre-eclampsia), in low and middle-income country (LMIC) populations.
Primary Objective	To determine whether the CRADLE package reduces a composite of (all-cause) maternal mortality or major morbidity by ≥25%, in ten LMIC areas.
Trial Design	This is a two-phased multicentre stepped wedge cluster randomised controlled trial of the introduction of the CRADLE package (Vital Signs device and training package) to maternity care settings in LMICs.
Outcomes	• Maternal death • Eclampsia • Hysterectomy
Eligibility Criteria	All pregnant/postpartum women living in Trial Area catchment areas* within the trial time frame. **Inclusion criteria**: women identified as pregnant or within the 6 weeks post-partum period, presenting for antenatal, intrapartum or postpartum care. There will be no **exclusion criteria**.
Intervention	CRADLE VSA Microlife device and Training Package
Time Frame	Anticipated start date: November 2015 Anticipated end date: January 2018

2. Background

We have developed a simple, accurate, handheld device to measure blood pressure and pulse. This device has some special features that make it ideal for use in both clinic and the community in low and middle-income countries. One of these features is the 'traffic light' system; the device tells the user if the blood pressure and pulse measurements are

normal (green), worrying (yellow) or severely abnormal (red). This enables the device to signpost women who are unwell or becoming unwell. This will enable more appropriate and earlier referral to higher-level care. The device has been tested extensively and is shown to be accurate in pregnant women, even those with blood pressure problems.

3. Aims

The aim of this trial is to introduce this device with a training package to communities and clinics in ten different sites to determine whether this can reduce rates of maternal death and severe morbidity.

4. Trial Design

This is a two-phased multicentre stepped wedge cluster randomised controlled trial of the introduction of the CRADLE package (Vital Signs device and training package) to maternity care settings in LMICs. This is summarised in Appendix A.

Phase 1 commences 01/11/15 until 31/01/16.
Phase 2 commences on 01/03/16 until 31/01/18.

In Phase 2 each of the sites will collect all of the primary and secondary outcomes alongside some basic background information for the area. Each site will receive the intervention (CRADLE VSA and training package) at a designated time that will be randomised. We will inform you of this time from March 2016 after the completion of Phase 1. It could be any time between June 2016 and December 2017. This is a pragmatic trial therefore this document is to guide the implementation and data collection, but you should feel free to adapt data collection tools and registers or utilize existing tools in your catchment area.

5. Participants

a. Eligibility, inclusion and exclusion criteria

Population: all pregnant/postpartum women living in Trial Area catchment areas* within the trial time frame.

Catchment areas will be defined by local investigators and include all possible outreach facilities that result in women being assessed and referred to a defined central facility/ies, prior to randomisation and remain constant throughout the study period.

Inclusion criteria: women identified as pregnant or within the 6 weeks post-partum period, presenting for antenatal, intrapartum or postpartum care.

There will be no **exclusion criteria**.

b. Consent

Due to the design of this trial and the introduction of the CRADLE VSA device into routine antenatal care individual patient consent is not required for this trial and this has been approved by each site, ethics board.

For all interviews and focus group discussions written consent should be sought from the HCPs involved. Soft copies of the consent forms will be circulated, and hard copies are contained in this folder. It is important that all the HCPs involved in this stage are provided with the provided information sheet, or that it is read to them if needed, and that they are given a reasonable time to consent to being involved. Each HCP should be

given the opportunity to withdraw from participation at any point both during the data collection and for up to four weeks following data collection. Please check that involvement of each HCP is approved by their direct manager.

6. Interventions

The interventions are:

a) Microlife CRADLE Vital Sign Alert Device

The Microlife CRADLE VSA is one of the few BP devices to have been validated as accurate in pregnancy (including pre-eclampsia) and the only one validated for women with low BP. The device fulfils the World Health Organisation requirements for low-resource settings. Other unique developments suited to LICs include a micro-USB charging ability and "traffic light" early warning system for hypertension and shock (secondary to either obstetric haemorrhage or sepsis).

Figures 1&2 – The Microlife CRADLE VSA (figure 1: showing shock warning, figure 2: showing hypertension warning)

b) Training programme

Everyone who uses the device will need to be trained. This may include community HCPs, nurses, midwives, general physicians, primary care physicians and obstetricians at the community and primary to tertiary facility levels. We have developed a simple Microlife CRADLE VSA training programme appropriate for all levels of HCP.

The programme consists of an animated video, posters and information tags attached to the device. There are two versions of these materials, one for community staff without medical training and one for skilled healthcare staff of any level.

7. Outcomes

a) Primary outcomes

The primary outcomes are:

- **Maternal death** = death during pregnancy or within 42 days of delivery.
- **Eclampsia** = generalised convulsions or coma with increased BP during pregnancy, labour or within 42 days of delivery in the absence of epilepsy or another condition predisposing to convulsions.
- **Emergency Hysterectomy** = surgical removal of all or part of the uterus

Note: We do not expect every patient to be followed up for 42 days after discharge from hospital to ensure they remain well. If they are alive and well on discharge you can presume they stay well unless you become aware of an outcome through hospital admissions or events in the community.

b) Maternal Secondary Outcomes

- Intensive Care Admission = admission (or referral to) to a separate ward or room with higher level of care than the main clinical area.
- Stroke

- Cause of ICU admission
- Cause of maternal death
- Cause of emergency hysterectomy
- Place of first eclamptic fit
- Place of death

c) Neonatal Secondary Outcomes

- Number of stillbirths
- Number of early neonatal deaths (< 7 days)
- Number of late neonatal deaths (7-28 days)

d) Facilities and Resources Baseline Data = Start of Trial only

- Number of primary care facilities: First point of access e.g. District clinic
- Number of secondary care facilities: First referral point e.g. District hospital
- Number of tertiary care facilities: Highest referral centre e.g. Regional hospital
- Distance of each facility from the nearest tertiary centre (km)
- Number of doctors in each facility
- Number of doctors with obstetrics and gynaecology speciality training in each facility
- Number of anaesthetic doctors in each facility
- Number of nurses/other HCP with anaesthetic training in each facility
- Number of midwives in each facility
- Number of nurses with midwifery training in each facility
- Number of clinical officers in each facility
- Number of traditional birth attendant or community volunteers within catchment area engaged with the trial.

- Capacity for blood transfusion
- Availability of Magnesium Sulfate
- Number of ICU beds: as defined above
- Number of working blood pressure devices

8) Monthly Data

- Number of Deliveries
- Number of Caesarean sections
- Number of Assisted Delivery
- Any change in the facilities and resources baseline data
- Number of people trained to use the CRADLE VSA
- Number of CRADLE VSA given to each facility
- Number of broken/lost CRADLE VSA

To be completed after implementation only

8. Data Collection

a) Collection Methods

The best method of data collection should have been determined during Phase 1.

It is most important that every outcome from community, clinics and hospitals are included. The trial will not work if data is only collected from one source.

It is very important that the main outcomes are collected in the same way at the start of the trial (01/03/2016) and throughout the trial duration no matter when the intervention is implemented.

Important things to note:

If one patient has multiple events e.g. an emergency hysterectomy and admission to intensive care, these should both be included on the same entry. The KCL team will determine which outcomes will be analysed.

As patients that are unwell in the community are likely to be transferred to hospital, it is important that their outcomes are not duplicated in the records. For example, the clinic HCP may complete an outcome form for a patient that has an eclamptic fit in the community. If this patient is moved to hospital, they may also complete a form. It is important to make sure that the patient is only entered **once** onto the database. They may be recognised as duplicated because they have the same initials/year of birth and date of outcome, but if it is unclear you may need to contact the clinics to clarify events. There is space on the paper form to enter a patient name or unique patient number. Please enter the study ID number from the MedSciNet onto the paper form so that if any later amendments are required the patient can be located on the database easily.

b) Paper Data Collection

As the research assistant will be travelling between facilities they will need to record these outcomes on the paper data outcome form provided in **Appendix B**. It may help to give a modified version of these forms or a specific book to the clinics for HCP's to complete but the research assistant will then need to visit each clinic on a regular basis (e.g. weekly) to verify these outcomes and include them in their own accurate and fully completed master copy.

It is the research assistants' responsibility to then transfer this information to the online database regularly (i.e. once a week). The following section will describe how to do this. Following this the paper documents should be stored in a secure filing system that can

only be accessed by the research team and HCP. Each research assistant should monitor security and confidentiality on a monthly basis.

c) Online Data Management

The website for online data collection is: www.medscinet.com/cradle3

A separate document with detail of the updated MedSciNet will be provided

d) One-Off Additional Data

Two periods of 4 weeks referral monitoring at each facility

We hypothesise that the introduction of the CRADLE VSA into routine care will increase the number of women receiving treatment and referral. It is not possible to compare the number of referrals across all sites for the duration of the trial. Therefore, we are asking each site to complete a record of how many maternity patients they see and how many maternity referrals are made for a period of 4 weeks before and after the implementation.

The first 4-week period should be undertaken in the month prior to implementation (so that data collection tools can be distributed at the same time as sensitisation for implementation). The second 4-week period should be undertaken three months after implementation, so there is sufficient time for the device to truly be incorporated into care.

The most important information from this is the proportion of women seen that are referred to hospital, if possible we would also like to gather details regarding the cases referred. The form below can be supplied to facilities to support this collection if existing tools do not exist already.

At the end of the one-month monitoring the research assistant(s) will need to calculate the total number of women seen, total number of referrals to hospital, total cause of referrals and mode of transport. This data should be sent to the trial coordinator.

9. Economic Evaluation

A simple cost-effectiveness analysis will be undertaken to inform future scale-up of the device. During the trial you will need to provide information on:

- Cost of facilitating central training session (room hire, transport, subsistence etc.)
- Cost of facilitating peripheral training
- Salary of training personnel
- Non-clinical supplies required to support training
- Cost of support training visits

This data should be entered onto the excel document called “Economic Evaluation CRADLE 3”. We need to estimate the cost of the training *but not the cost of running the trial*. Although a lot of the activities will be combined please try to make a note of how much time is spent on training support after implementation (i.e. not data collection or data entry). An estimate of the total time spent on training support each week can be entered onto the appropriate tab on the excel. We also need to determine the cost of trial staff to implement the training specifically. Please enter the total staff costs onto the spreadsheet. We appreciate that many CRADLE staff also undertake other research or clinical roles therefore please enter the percentage of the staff role that is allocated to CRADLE. That KCL team can estimate the costs from this.

10. Monitoring

The research assistant(s) will need to monitor the consistency and quality of outcome data at each area (monthly). The trial coordinator will monitor data entry by each research assistant continuously on MedSciNet. The trial coordinator will be able to filter and identify any problem areas and discuss these during monthly phone calls.

a) Data Verification

The PI is required to check approximately 10% of the source data to check for transcription errors. This means that for every 50 outcomes recorded by the research team the PI should check five entries against their source such as the register or patient record. This process should be reported back to the trial coordinator during the monthly monitoring meetings.

b) Monthly monitoring meetings

We would like to have regular informal contact to discuss any problems, provide support and training. This can be via emails, skype, calls or messaging. In addition, we will arrange monthly meetings between the KCL research team and your team including the PI to discuss progress.

At the start of Phase 2 the method of data collection will be confirmed for each facility within the catchment area. This will be agreed by both the local research team and KCL team. Every month we will schedule a brief meeting. During this meeting, there will be opportunity for the local research team to raise any queries.

In addition, the following will be discussed:

- Any deviation from the agreed method of data collection
- Any changes to staff e.g. new staff employed to cover maternity
- Any policy/structural changes e.g. new referral processes, new costs to patients
- Any new projects or research that may influence outcomes
- Any geographical changes e.g. flooding meaning that the research assistant(s) were unable to complete visits.
- The outcome of the data verification by PI
- Confirmation of plans for the implementation stage
- Any data queries
- Details of any issues with devices

After implementation, we will be asking the research assistants about the level of support that they have been able to provide to the HCPs. We would like the research assistants to attend the phone calls at least once every two-months post-implementation.

10. Implementation

Each trial area will receive an appropriate number of CRADLE devices and large blood pressure cuffs according to the area size, number of facilities, number of HCPs and delivery rates of the area. These will have been determined by the CRADLE team and local PI prior to the start of the trial. We will provide a label printer and methods to secure the devices. At the randomised time point the blood pressure devices previously in use must be removed from the clinical areas and stored in a secure area. The CRADLE devices and the CRADLE training programme will need to be distributed to all HCPs caring for pregnant/postpartum women. It is important that the intervention is implemented across the entire area as quickly as possible. Disseminating the devices and training staff should take no longer than one or two weeks for the entire area in the first instance. Ongoing training (e.g. for new staff, staff unable to attend central training

sessions) will be given by the local research assistant(s). Additional support that extends beyond this will be provided remotely by the CRADLE team and from the research assistant(s) in the area.

The KCL CRADLE Team (Nicola Vousden +- Elodie Lawley / Andrew Shennan / Hannah Nathan) will travel to your site to help with implementation. The first days of their visit will involve detailed discussions with the local research team. It is important that the local team are well trained and supported so that they are confident to deliver the training, interviews and trial monitoring at their facilities. The KCL team will be present to provide support.

Central Training Sessions

We recommend that you hold a central training session for representative staff from each hospital and clinic. This may be the sister in charge of the ward, the matron or key leader of a clinic. In this session detailed training about the device use and maintenance will be disseminated over 1-2 hours. Holding detailed group sessions for key staff from each clinic will mean that uptake and use of the device will be faster as they can act as local trainers to their teams. The research team should facilitate these sessions with support from the PI and KCL team. A **'User Manual'** will be provided. A copy should be given to each attendee so that they can act as the CRADLE lead for their clinical area. Where possible the training video should also be provided to the CRADLE leads on their phone.

At central training, attendees should be trained sufficiently to enable them to train new staff or staff that were unable to attend training sessions. In this way, the training can be sustained throughout and beyond the trial period.

Practical tips

We will provide a presentation to be used at central training sessions. Where possible this should be projected onto a large screen. Depending on the size of the room and number of staff attending, it may help to set the room with small tables and groups of about six around each table. If this is not possible, arrange the room in a semicircle to encourage discussion. Try to avoid large rooms of forward-facing rows where possible, as the teaching is practical with group discussions and use of the device in small groups.

For each training session, you will need:

- The films uploaded ready to show
- The training presentation with method to display to the group
- CRADLE VSA devices
- Training Register
- Device Register
- Training Checklist

Peripheral Training Review

To ensure the training for the CRADLE VSA is being disseminated by the CRADLE leads for each clinical area, you should also attend every clinical area. This gives an opportunity to check knowledge transfer, secure the devices and remove old devices. As a minimum, all staff using the CRADLE VSA should have seen the film. Appendix D shows a prompt to facilitate the peripheral review.

Ongoing Facility Support

We know that the amount of support required will vary between sites. As a minimum, we would like the research team to once a month review the use of the device, enquire about any problems with the CRADLE VSA and report any action taken to resolve these problems. This can be reported back to the KCL team at the monthly meeting. New staff should ideally be trained, using the film and training materials, by the CRADLE lead of

that clinical area that attended the central training session or a designated colleague. The research team should encourage this. If this doesn't happen then the research team should also ensure that all new staff have viewed the film.

Are the devices being used?

Have you experienced any problems with the devices?

What has done been about these problems?

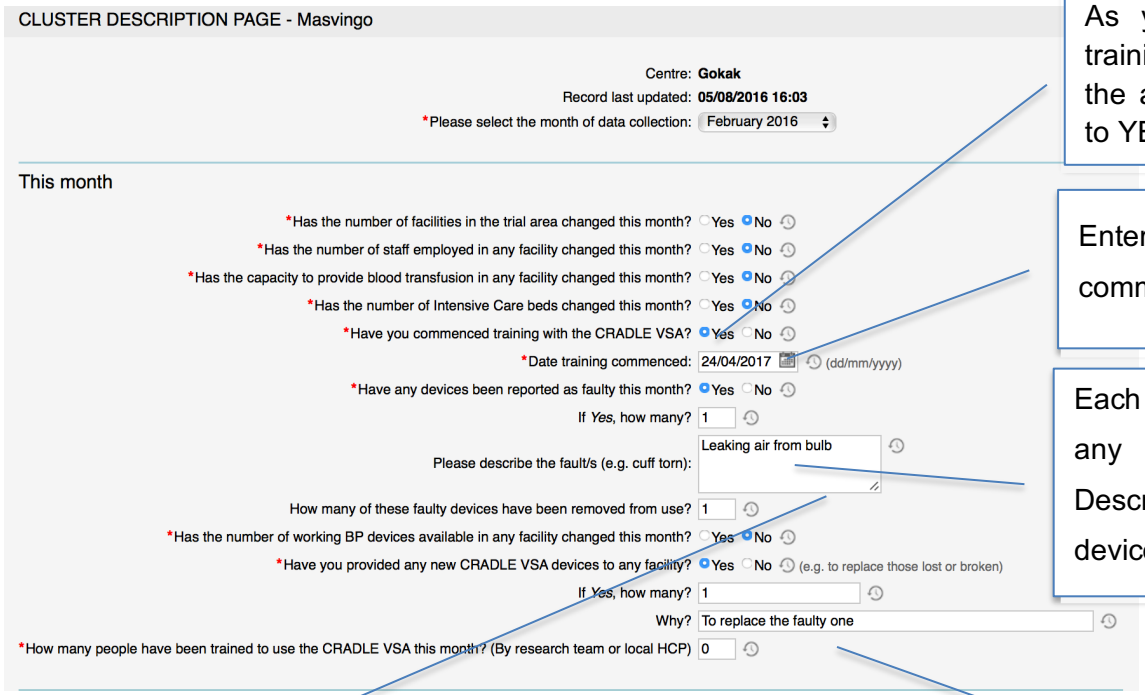
Implementation Data

There are a number of process measures that we will measure during implementation. These are:

- The proportion of staff trained
- The number of VSA devices disseminated to each area and the number of working BP devices prior to implementation
- The number of VSA disseminated after implementation (e.g. to replace lost or stolen)

The KCL team will ensure that this data is collected during implementation (either on provided forms or site-specific form). Following completion of training this information should all be entered onto the MedSciNet. Instructions are below:

When you complete the Cluster Description Page for the month of implementation you should enter the date of training, the number of staff trained and the number of CRADLE VSA disseminated. These are shown below:



As you have commenced training this month change the answer to this question to YES

Enter the date that training commenced

Each month collect and store any devices reported faulty. Describe the fault of each device here.

In the month of implementation, the answer should be 'Yes' and the total number of VSA disseminated should be written here. In subsequent months write the number of any additional of VSA distributed and describe e.g. to replace a lost/faulty device.

In the month of implementation enter the total number of people trained here. In subsequent months enter any additional people trained – most people will be shown by colleagues but if there are specific sessions held these should be counted.

The other points can be added to the Health Care Facility table. The steps are below:

- Check that the 'number of working blood pressure devices' for each facility for the *month prior to implementation* is correct.
- Check that the number of staff (doctors, nurses, volunteers, midwives etc.) is correct for the month of implementation.
- Change the 'number of working blood pressure devices' to reflect the number of CRADLE VSA disseminated to each facility. If a facility is still using their old blood pressure machines in addition to the CRADLE VSA then this value should reflect the number of working blood pressure machines prior to implementation + the number of VSA given. Please let Nicola know the names of facilities where this is the case, so it can be discussed.

10. Interviews and Focus Groups

The aims of the interviews are to explore the experience of triage, on-site intervention, referral and transportation and reception at the higher-level facility. In addition, the escalation process from clinic and community to hospital level care and barriers to care will be explored. In total, we would like you to undertake up to five interviews. You should start by selecting around three HCPs from a variety of sites and experience to be interviewed. These HCPs should be directly involved in care of pregnant women. You can then work together with the trial coordinator to identify any themes and select further participants based on this.

We would also like the research team to arrange a focus group of 5-8 participants in order to map the management pathways in your area and to determine if use of the CRADLE VSA has impacted on these pathways and how. Try to identify participants that are key in deciding who is referred, at the receiving end of referrals in the hospitals and appropriate managers.

These interviews and focus groups should be carried out in the third month following implementation.

If you are implementing prior to October 2017 we would also like you to undertake a second focus group 6-9 months after implementation for 5-8 participants. The purpose of this focus group is to determine if the use of the CRADLE VSA and the ongoing training varies over time. Try to identify participants that have different experience with the CRADLE VSA for example both CRADLE leads, HCP that attended implementation training and new HCP that experienced peer training.

For the interviews and focus groups contact the line managers in each facility to help identify potential participants and gain their approval. Provide potential participants with the appropriate information leaflet and after they have had time to review this then ask them to provide written consent on the specific forms given.

For each interview and focus group please complete the attendees' details on the form in Appendix E, F and G. We have provided a sheet of questions that can be used as prompts for the interviews and focus groups (Appendix E, F and G). They do not need to be followed in order and you may wish to change the wording if you find it more natural. After they have been completed, please translate all the interviews and focus group and transcribe into a word document. Please send these documents to Nicola.vousden@kcl.ac.uk.

Tips for the undertaking Interviews and Focus Groups

Feel free to explore topics if they arise, the questions provided are a prompt not a script.

Prompt the participant to explore their answer by asking *"Why?" "In what way?" "Can you give an example?"*

Encourage everyone to participate in the focus group.

This should not last longer than one to two hours.

If you have any concerns or queries about any of the answers given, make sure to wait until *after* the session to address these in order to maintain a natural conversation.

11. Contacts

CRADLE Trial Team at KCL

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Summary of events

Daily from March 1st	Start of Phase 2 data collection.
	Complete Facility and Resource data table on MedSciNet.
Every month	Complete baseline data questionnaire on MedSciNet.
	Speak with KCL team during monthly monitoring meeting.
4 weeks before implementation	Collect data on referral rates for 4 weeks either by distributing form or using existing registers.
Randomised time point (between 1st June 2016 and 1st November 2017)	Implement the intervention.
3 months after implementation	Collect data on referral rates for 4 weeks either by distributing form or using existing registers.
	Organise focus group with 5-8 Health care Providers.
	Organise interviews for 5 Stakeholders.
6-9 months after implementation	Organise follow up focus group with 5-8 Health care Providers
January 31st	Complete data collection.

Sample primary and secondary outcome data collection tool

Initials:		Other Patient Identifier:	
Date of birth:		Patient Study Number:	
Referred from:			
Eclampsia	Yes ☐	Date of first Fit	
	No ☐		
	Community ☐ Clinic ☐ Hospital ☐		
Hysterectomy	Yes ☐	Date of Hysterectomy	
	No ☐		
	Ruptured uterus ☐ PPH ☐ Sepsis ☐ Other (describe):		
Maternal Death	Yes ☐	Date of maternal death	
	No ☐		
	PPH ☐ APH ☐ Stroke ☐ Eclampsia ☐ Pre-eclampsia ☐ Gynaecological sepsis ☐ Obstetric sepsis ☐ Other sepsis ☐ Other (describe):		
Stroke	Yes ☐	Date of stroke	
	No ☐		
ICU Admission	Yes ☐	Date of Admission	
	No ☐	Number of days	
	PPH ☐ APH ☐ Stroke ☐ Eclampsia ☐ Pre-eclampsia ☐ Gynaecological sepsis ☐ Obstetric sepsis ☐ Other sepsis ☐ Other (describe):		
Gestation ≥ 28^{+0} weeks	Yes ☐		
	No ☐		
Delivered (if ≥ 28^{+0} weeks)	Yes ☐	Date of delivery	
	No ☐		
	Alive ☐ Stillbirth ☐ Early NND ☐ Late NND ☐		

Sample referral monitoring data collection tool

Date:	10/02/16	
How many maternity patients have you seen today?	12	
How many maternity referrals made today?	1	
If referrals made please complete the following details		
Reason for referral	Did you give medications?	How did she travel?
Infection / bleeding / high blood pressure / labour/ other:	Misoprostol	Ambulance / taxi/ public transport / foot / did not attend / other
Infection / bleeding / high blood pressure / labour/ other:		Ambulance / taxi/ public transport / foot / did not attend / other
Infection / bleeding / high blood pressure / labour/ other:		Ambulance / taxi/ public transport / foot / did not attend / other

7.3 Interview and Focus Group Guides

Interview Questions

The aim of the interview is to explore the experience of triage and escalation of care. Reassure the interviewee their answers will be anonymous, and we would like them to be honest. These questions are a guide only; feel free to explore topics as they arise.
Introduction questions: These are designed to help the participant to relax. The answers do not need to be detailed. This section can be brief.

- How long have you been using the CRADLE VSA?
- What were you using before the CRADLE VSA? How does it compare?
- How often do you use the CRADLE VSA?
- What did you think about the training package?

Exploring questions: encourage participants to explain their answers by asking 'Why?' 'How?' 'In what way? Encourage them to give specific examples from their practice.

- What do the women think about the CRADLE VSA?
- Has using the CRADLE VSA affected your routine care of antenatal patients?
- Has it affected the *diagnosis* of patients with pregnancy problems?
- Has it affected your *management* of women with pregnancy problems?
- If you are looking after an unwell woman that you think needs a higher level of care, please can you explain in detail the actions that you would take (i.e. refer a woman to hospital)
    - Who do you speak to? How do they respond?
    - What actions do you take?
    - What does the patient need to do?
    - How long does this take?
    - What other factors influence this process?
    - What influences the women's decision to follow your advice?

- Has this changed since you've been using the CRADLE VSA?
- Has it made any of these steps more difficult?
- Has it made any of these steps easier?
- Are there times that you manage a woman's care differently to the suggested traffic light guidance?
- Can you please describe one or more of these cases and the reasons why?

Focus Group

The aim of the focus group is to map the management pathways in your area and to determine if use of the CRADLE VSA has impacted on these pathways and how. Reassure the participants their answers will be anonymous, and we would like them to be honest. These questions are a guide only; feel free to explore topics as they arise.

If you have any concerns or queries about any of the answers given, make sure to wait until *after* the session to address these in order to maintain a natural conversation.

- How long has the CRADLE VSA been in use in your area?
- Can you describe the pathway for a pregnant woman who is feeling unwell at her home?
    - Where does she go first?
    - Who does she see?
    - What measurements are taken?
    - Who decides what action is taken? Who takes this action?
    - If she needs referral who decides? Where is this recorded? How is the referral made?
    - When she arrives to referral unit, who sees her? what happens next? why?
- How many steps are there for the patient?

- How long does each step take?
- What are the problems for patients?
- What are the problems for staff?
- Have any of these processes changed since the introduction of the CRADLE VSA? *(In what way? Why?)*
- Have the number of referrals to the hospital changed? *(In what way? Why?)*
- Has the way that patients are treated changed? *(In what way? Why?)*
- Has the CRADLE VSA had any impact on the work load of staff? *(In what way? Why?*

7.4 Ethical Approval

Country	Cluster Primary Investigator and Affiliation	Ethics Approval Authority	Ethics Approval Number
Ethiopia	Adrian Brown, Maternity Worldwide.	Ethiopian Public Health Institute, Ethiopia	EPHI6.4/185
Zimbabwe	Francis Gidiri, University of Zimbabwe.	Medical Research Council of Zimbabwe; Zimbabwe.	MRCZ/A/1999
Sierra Leone	Matthew Clarke, Welbodi Partnership, Freetown.	Office of the Sierra Leone Ethics and Scientific Review Committee Directorate of Training and Research, Connaught Hospital; Sierra Leone	Not provided
Haiti	Carwyn Hill, Hope Health Action, Cap Haitien	Cap Haitien does not have a formal ethical review process, Memorandums of understanding were drawn up with each hospital trust and a letter of support gained from the Ministry of Health.	NA
India	Mrutyunjaya Bellad, Jawarharlal Nehru Medical College, KLE University, Belgaum.	K.L.E Society's Jawaharlal Nehru Medical College, Belgaum, India	MDC/IECHSR/2015-16/A-59; KLEU/EC/2016-17/A-95; KLEU/EC/2017-18-A-104
Zambia	Bellington Vwalika, University of Zambia, Lusaka; Sebastian Chinkoyo, Ndola Teaching Hopital, Ndola.	ERES Converge; Zambia	20215-Aug-008
Malawi	Grace Makonyola, Maternity Worldwide.	National Health Sciences Research Committee at Zomba Central Hospital, Malawi	NHSRC 15/11/1504
Uganda	Julius Wandabwa, Sanyu Africa Research Institute, Mbale; Josephat Byamugisha, Makere University.	Uganda National Council for Science and Technology; Uganda	HS1953

7.5 Additional funding awarded

Title of Clinical Trial	**CRADLE-4: Can Reduction of Adverse Pregnancy Outcomes occur with Planned Delivery vs. Expectant Management in Pre-eclampsia?**
Amount awarded	£999,417.94
Funding Period	36 months
Funder	Global Research Programme: Department of Biotechnology India, Medical Research Council, Economic and Social Research Council, Newton Fund, UKAID; MR/R021376/1
Sponsor Name	King's College London
Chief Investigator	Professor Andrew Shennan
Co-investigators	Nicola Vousden, Jane Sandall, Paul Seed, Lucy Chappell
Purpose of the Trial	In low and middle-income country populations, does planned early delivery in women with pre-eclampsia between 34^{+0} and 36^{+6} weeks of gestation reduce maternal complications without increasing adverse neonatal outcomes compared to current practice?
Trial Design	This is a pragmatic multicentre randomised controlled trial across Karnataka, India and Lusaka and Ndola regions in Zambia. The main trial (Phase 2) will be preceded by a 6-month formative trial development period (Phase 1).
Outcomes (All components of composites will be confirmed if feasible during Phase 1)	Primary Maternal Outcome: • Composite of outcomes during pregnancy or until 42 days post-delivery: Maternal morbidity: death, stroke, eclampsia, pulmonary oedema, respiratory failure, hepatic dysfunction, acute kidney injury, severe hypertension Primary Perinatal Outcome: • Composite of still birth, early and neonatal death, severe morbidity (respiratory distress syndrome, neonatal seizures, neonatal unit admission, coma) Secondary outcomes: • Mode of delivery • Individual components of primary outcomes • Process measures • Patient and family satisfaction with care • Cost-effectiveness evaluation
Eligibility Criteria	Inclusion criteria: • Pregnant women between 34^{+0} and 36^{+6} weeks of gestation inclusive • Pre-eclampsia (as defined by internationally recognised criteria as the onset of a new episode of hypertension over 20 weeks of gestation with substantial proteinuria or organ dysfunction) • Able to give consent • Viable fetus(s) Exclusion criteria: • Urgent need to deliver within the next 48 hours (exact criteria to be determined during Phase 1)
Intervention	Women accurately diagnosed with pre-eclampsia (using VSA) at >34 weeks gestation will be randomised to planned early delivery (initiated within 48 hours of randomisation). This will entail delivery by the mode indicated for obstetric reasons (e.g. by induction of labour, or by Caesarean section).

Title of Study	**HAPPEE: Humanities and Arts in Preventing Pre-eclampsia complications through community Engagement and Education**
Amount awarded	£176,532.00
Funding Period	24 months
Funder	Medical Research Council and Arts and Humanities Council MC_PC_MR/R024510/1
Sponsor Name	King's College London
Chief Investigator	Professor Andrew Shennan
Co-investigators	Nicola Vousden, Tanya Robbins, Ann Kelly, Mickias Musiyiwa, Carwyn Hill, Jamie Bell, Jane Sandall
Purpose of the Study	The aim of the HAPPEE project is to develop sustainable and synergistic interdisciplinary and international academic relationships. Through this robust network we aim to raise awareness and improve education around pre-eclampsia whilst furthering our understanding using arts and humanities in community engagement in diverse contexts.
Study Design	Phase 1 involves exploring context and undertaking qualitative work in Zimbabwe and Haiti. This will involve formal stakeholder analysis, collecting baseline information regarding maternity care structures locally and exploring local priorities, values, social structures, the role and power of decision makers, religious and cultural contexts regarding pre-eclampsia in each country. Each country will undertake face-to-face semi-structured interviews (n=20) and focus groups (n=6) until data saturation is reached. Phase 2 of the project involves the development of culturally relevant and context specific educational materials. This will build upon existing community engagement maternal health work and will be developed with direct input from community members. We envisage these may be in the form of short animations, videos, body maps and community interactive theatre.